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THE UNIVERSITY OF ALBERTA

STUDIES ON THE CHEMISTRY OF 1,2-DIHYDROPYRIDINES

by

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My Family

ABSTRACT

Reaction of the ambident anion *N*-lithio-2-*n*-butyl-1,2-dihydropyridine (LXXXIb) with several electrophilic reagents has been investigated. Treatment of LXXXIb with methyl chloroformate afforded *N*-methoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (LXXXIVb) and 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (CXIXb). Reaction of *N*-lithio-2-methyl-1,2-dihydropyridine (LXXXIa) with methyl chloroformate afforded the corresponding 2-methyl analogs. Reaction of LXXXIb with 3-ethoxycarbonylpyridine (CXVIIIc) afforded 2-*n*-butyl-5-(3'-pyridylcarbonyl)-1,2-dihydropyridine (CXXc) and 2-*n*-butyl-5-(3'-pyridylcarbonyl)-pyridine (LXXXVc). The reaction of LXXXIb with 4-methoxycarbonylpyridine (CXVIIId) and 2-ethoxycarbonylpyridine (CXVIIIe) afforded similar 5-substituted products.

Catalytic hydrogenation of *N*-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) and CXIXb with 10% palladium-charcoal and hydrogen gave *N*-methoxycarbonyl-2-phenylpiperidine (CXXV) and 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2,3,4-tetrahydropyridine (CXXVI) respectively.

Treatment of *N*-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) with lithium diisopropylamide and iodomethane afforded *N*-propionyl-2-phenyl-1,2-dihydropyridine (CXXXI, R = Me).

The Diels-Alder reaction of *N*-substituted-1,2-dihydropyridines XXXIXa, c, and d, LXXXIVb, CXIXb, LV, and CXXXVII with 1,2,4-triazoline-3,5-diones CXXXVIIIa-c afforded *endo* [4+2] cycloaddition products. *N*-Acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) reacted with CXXXVIIIa-c to afford a mixture of stereoisomers 5-*endo*-acetyl-

6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenyl (ethyl, hydrogen) imide, CXXXIX and 5-*exo*-acetyl-6-*endo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenyl (ethyl, hydrogen) imide, CXL. On the other hand, N-methoxycarbonyl, methanesulfonyl, ethoxycarbonyl, or benzoyl-1,2-dihydropyridines gave CXXXIX as the exclusive product. The stereochemistry assigned to the cycloadducts was based on nmr spectral data and particular use was made of the anisotropic effects of the C-7, C-8 unsaturation on the R^1 and R^2 substituents of the cycloadducts. Similar results were obtained in reactions employing maleimides, CLVIa-c, as the dienophile. The stereochemistry of the cycloadducts was assigned on the basis of the magnitude of the coupling constants for the protons at the bridgehead positions (C_1-H, C_4-H) and the adjacent protons (C_2-H, C_3-H) as well as the anisotropic effects of the C-7, C-8 unsaturation. Aluminum chloride catalyzed the reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with maleimide (CLVIc) and N-methylmaleimide (CLVIb). The reaction of XXXIXb with 4,4-diethyl-1,2-pyrazoline-3,5-dione (CLIV) gave 5-*endo*-methoxycarbonyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-diethylmalonimide (CLV).

Treatment of N^{10}-substituted-10H-pyrido[3,2-b][1,4]benzothiazines CLXXII with *n*-butyllithium and electrophilic reagents was investigated. Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) with *n*-butyllithium and methyl chloroformate gave 1-methoxycarbonyl-2-*n*-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIa) and 4-methoxycarbonyl-10-methyl-10H-pyrido[3,2-b][1,4]-

benzothiazine (CLXXXVIIa). Similar products were obtained from the reaction of 10-(3-dimethylaminopropyl)- and 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId and e respectively) with _n_-butyllithium and methyl chloroformate. Reaction of CLXXIIb with _n_-butyllithium and diethyl chlorophosphate gave 1-diethylphosphoryl-2-_n_-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIb), 4-diethylphosphoryl-10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXXVIIb), 2-_n_-butyl-4a-ethyl-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXXVIIIb), and 2-_n_-butyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXIIb). Similar products were obtained from the reaction of CLXXIId and e with _n_-butyllithium and diethyl chlorophosphate. Reaction of CLXXIIb with _n_-butyllithium and trifluoromethanesulfonyl chloride gave 4-chloro-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXVIId) and 2-_n_-butyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXIIId). Similar products were obtained from the reaction of CLXXIId with _n_-butyllithium and trifluoromethanesulfonyl chloride. Reaction of CLXXIIb with _n_-butyllithium and p-fluorobenzoyl chloride gave 2-_n_-butyl-4-(or 7-)p-fluorobenzoyl-10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXLc-1 or 2) and 1,4-(or 7-)di-p-fluorobenzoyl-2-_n_-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXXIXc-1 or 2). Treatment of 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIc) with _n_-butyllithium and methyl chloroformate gave 10-(2-N-methoxycarbonyl-2-N-methylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLIV) while reaction of CLXXIIc with _n_-butyllithium afforded 10-_n_-hexyl-10H-pyrido-

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Treatment of 2-anilinopyridine (CCXIIIa) with n-butyllithium and electrophilic reagents was investigated. Reaction of CCXIIIa with methyl chloroformate and acetyl chloride afforded 2-(N-methoxycarbonylanilino)-pyridine (CCXVI) and 2-(N-acetylanilino)-pyridine (CCXV) respectively. Reaction of CCXV with n-butyllithium and methyl chloroformate gave CCXVI.

Selected compounds have been subjected to broad spectrum pharmacological screening.

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1.0.0.0.0 Introduction

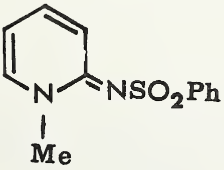
1.1.0.0.0 Pharmacological Significance of 1,2- and 1,4-dihydropyridines

To date there have been relatively few studies on the pharmacology of 1,2-dihydropyridines, so their therapeutic potential is yet to be realized. On the other hand, the biochemical importance of the 1,4-dihydropyridine portion of dihydronicotinamide adenine dinucleotide (NADH) is well known[1].

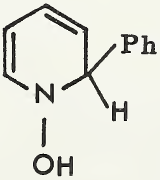
The NAD - NADH relationship will not be examined further other than to note that the presence of a 1,4-dihydropyridine ring in NAD stimulated the investigation of a variety of NAD model compounds[2-6]. This interest gave impetus to the development and pharmacological evaluation of 1,4-dihydropyridines which exhibited analgesic[8,11], spasmolytic[8-10], antineoplastic[12,13] and porphyria-inducing activity[14].

The most promising target appears to be the cardiovascular system where coronary-dilating[15-17] and hypotensive[18-22] properties have been observed. Certain 4,4^1-tetrahydrobipyridyl disulfamic acids have found use as herbicides and defoliants[23].

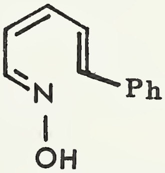
The pharmacological literature of 1,2-dihydropyridines is very sparse. The pyridoneimine I and N-hydroxy-2-phenyl-1,2-dihydropyridine (II), which was later shown to be the open chain compound III[26], have been reported to exhibit antibacterial properties[24,25].



I

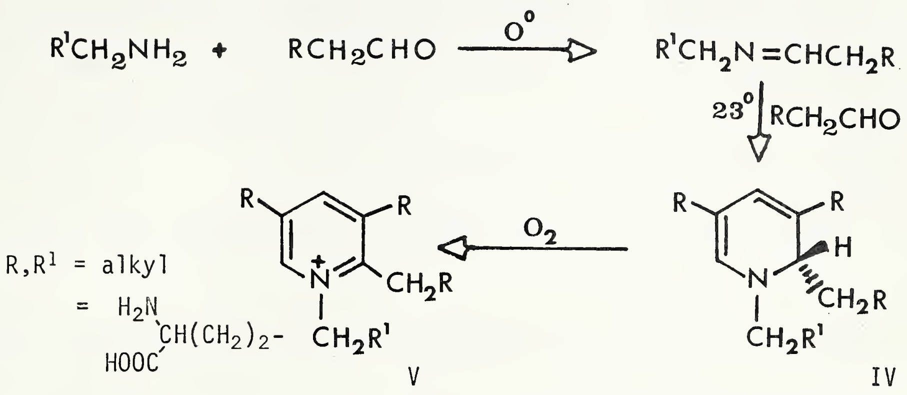


II



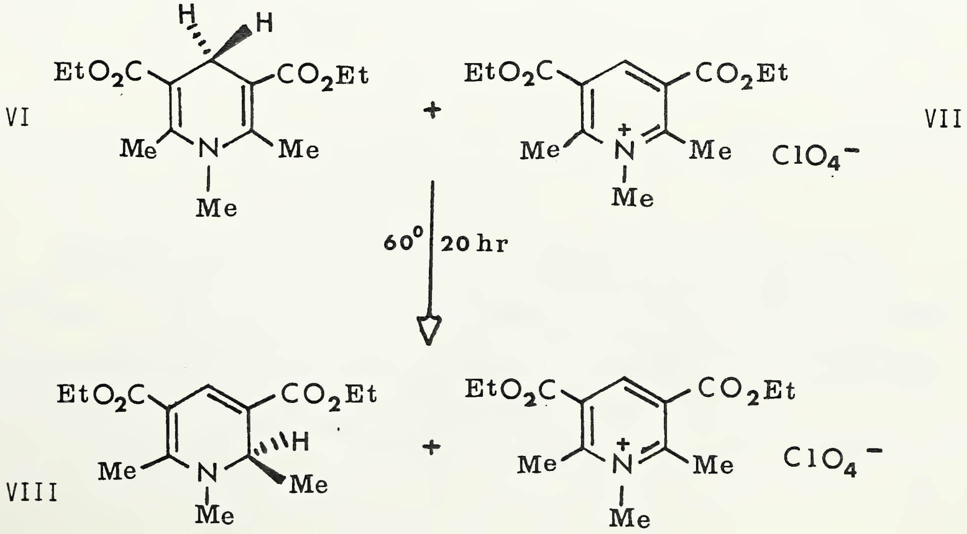
III

1,2-dihydropyridine model compounds, which are oxidized readily, are obtained from the non-enzyme catalyzed reaction of aliphatic aldimines with allysine analogs at room temperature. This observation supports



the biological involvement of a 1,2-dihydropyridine intermediate IV in the formation of desmosine and isodesmosine (V)[27]. The amino acids V are believed to form insoluble elastic fibers by crosslinking the polypeptide chains of elastin.

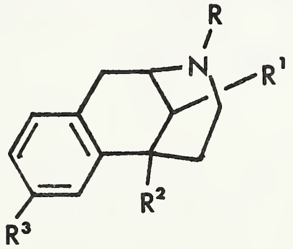
An interesting sidelight to the investigation of 1,4-dihydropyridines as NAD models is the detection of a 1,2-dihydropyridine VIII in a pyridinium salt - 1,4-dihydropyridine mixture[6,7]. This reaction



is catalyzed by the pyridinium salt VII and involves the transhydrogenation of the 1,4-dihydropyridine VI to the 1,2-dihydropyridine VIII. The reaction is irreversible under the conditions shown and substrate reduction is therefore prevented from proceeding to completion. At ambient temperatures the 1,2-dihydropyridine is not involved and the reductive process proceeds normally.

The mediation of a reactive 1,6-dihydropyridine species has been suggested in the biosynthesis of indole[28-30], nicotine and related alkaloids[32]. Büchi and co-workers[31] utilized a Diels-Alder cycloaddition reaction employing a 1,6-dihydropyridine for the first total synthesis of an iboga alkaloid. Synthesis of elaeocarpine required a 1,2-dihydropyridine intermediate[150].

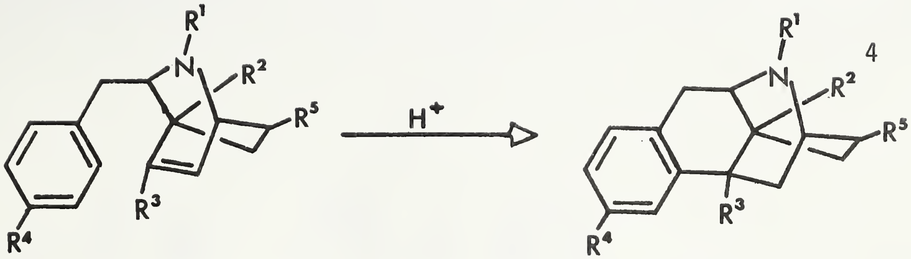
1,2-Dihydropyridines have been used as intermediates in the preparation of benzomorphan derivatives IX which possess analgesic activity[33]. These benzomorphan derivatives are related to the clinically significant narcotic analgesics pentazocine



IX

[R = $CH_2CH{=}C(CH_3)_2$, $R^1 = R^2 = CH_3$, R^3 = OH] and phenazocine ($R = CH_2CH_2Ph$, $R^1 = R^2 = CH_3$, R^3 = OH).

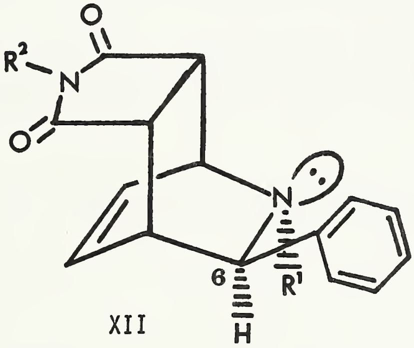
Ethanobenzomorphan derivatives XI have been shown to possess analgesic, antitussive, and anticonvulsant activity[34]. Acid catalyzed ring closure of benzylazabicyclooctenes X obtained from a Diels-Alder reaction using a 1,2-dihydropyridine afford XI.



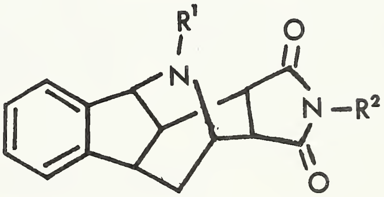
X XI

R^1 = alkyl, arylalkyl
R^2 = H, alkyl
R^3 = alkoxy
R^4 = H, alkoxy, OH, acyloxy
R^5 = Me, CH_2NH_2

An analogous cyclization of the Diels-Alder adducts XII prepared in our studies is prohibited by the exo-stereochemistry of the phenyl substituent at the 6-position. Furthermore, if reaction were possible, the newly formed ring would be cyclopentyl XIII rather than cyclohexyl.

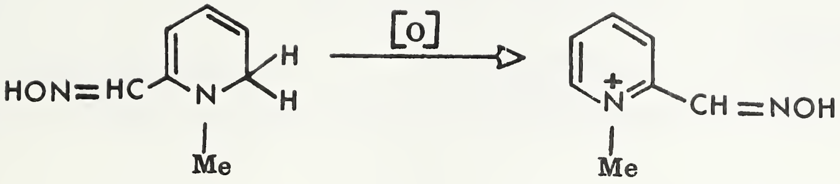


XII



XIII

Perhaps the greatest potential advantage of the 1,2-dihydropyridine system is its excellent physical-chemical characteristics which allow it to cross biological membranes which are impermeable to structurally related drugs. In this capacity they would act as prodrugs[37], to be "activated" at their site of action. This concept has been utilized in the delivery of a pyridinium salt XV across the blood brain barrier as the dihydropyridine derivative XIV. In vivo oxidation of the dihydropyridine affords the active drug XV[35].



XIV XV

In theory, this process may be applied to any drug which contains a quaternized heteroaromatic nitrogen. Although the argument has not been extended to biologically active pyridyl compounds, at least one study[14] has shown that both the dihydropyridine and corresponding pyridine compound were biologically active. The 1,2-dihydropyridine IV can also be considered as a pro-drug.

An extensive review concerning pyridines and reduced pyridines of pharmacological interest has recently been published[36].

1.2.0.0.0 Structure-Activity Relationships of Anticonvulsants

The anticonvulsant drugs currently available to the physician may be conveniently divided into the general categories of classic and novel anticonvulsants. The classic anticonvulsants are comprised of those agents whose pharmacology has been well established and which are, or have been, used on a routine basis. Included are the barbiturates XVI, pyrimidinediones XVII, hydantoins XVIII, acyl ureas XIX, oxazolidinediones XX, succinimides XXI, glutarimides XXII and amide derivatives XXIII and XXIV. The novel anticonvulsants are comprised of those agents which have seen application in other disease states but which have been accepted as adjuncts in

TABLE I

Anticonvulsant Drug Classes

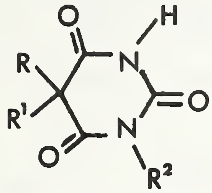
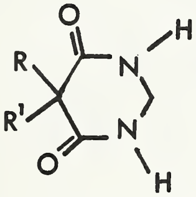
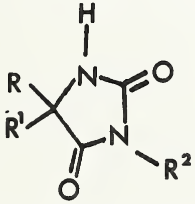
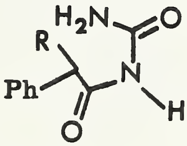
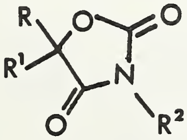
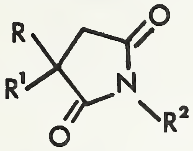
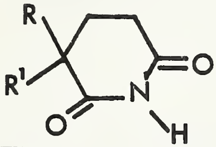
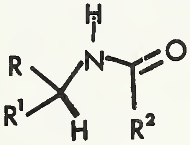
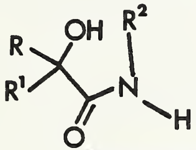
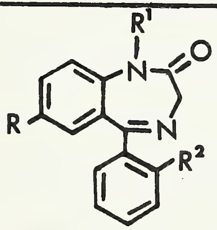
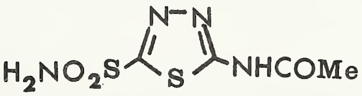
Anticonvulsant Class		Anticonvulsant Example	Substituents		
			R	R^1	R^2
	XVI	Phenobarbital	Ph	Et	H
	XVII	Primidone	Ph	Et	-
	XVIII	Diphenylhydantoin	Ph	Ph	H
	XIX	Phenacemide	H	-	-
	XX	Trimethadione	Me	Me	Me

TABLE I (contd)

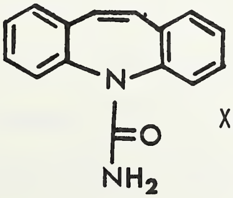
Anticonvulsant Class		Anticonvulsant Example	Substituents		
			R	R^1	R^2
	XXI	Phensuximide	H	Ph	Me
	XXII	Amino-glutethimide	Et	p-NH_2Ph	-
	XXIII	Benzchlorpropamide	H	Ph	CH_2CH_2Cl
	XXIV	Atrolactamide	Me	Ph	H



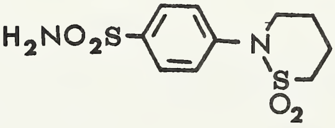
XXV



XXVII



XXVI

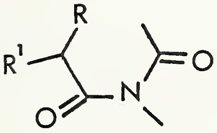


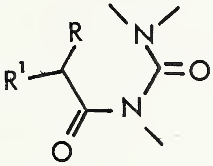
XXVIII

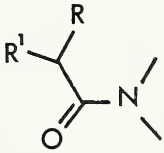
anticonvulsant therapy, and which have only recently come into routine (or investigational) use. Included are the benzodiazepines XXV, dibenzazepines XXVI, and sulfonamides XXVII and XXVIII.

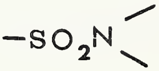
Examination of the structures shown in Table I reveals the presence of three important structural features; viz:

1. An imide XXIX, ureide XXX, amide XXXI, or sulfonamide XXXII moiety which is generally part of a cyclic system.


XXIX


XXX

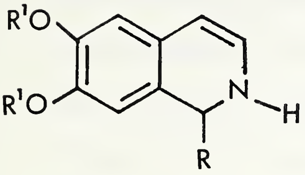

XXXI


XXXII

2. A disubstituted (R, R^1) carbon atom in which one substituent is generally aryl and the other short chain aliphatic.
3. A 1,3-dicarbonyl system.

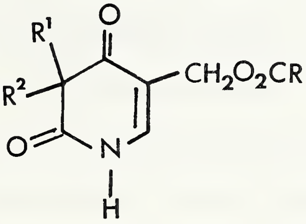
A review of the literature indicates that most anticonvulsants synthesized recently continue to incorporate these structural features[38] into a variety of cyclic systems. Benzodiazepines[39-41], pyridodiazepines[42-44], perhydropyridodiazepines[45], pyrrolidinediones[46], benzamides[47,48], indanediones[49], carbamates[50,51], pyrazolines[52], piperazines[53], indoles[54], sulfonamides[55-59], amides[60,61], hydrazides[62], and diphenylsilanes[63] are well represented. The dihydroisoquinolines XXXIII[64], tetrahydroisoquinolines[65], pyridinediones XXXIV[66], hexahydropyridopyridazines XXXV[67], tetrahydropyridines XXXVI[68], naphthenones XXXVII[69], and tetrahydrocannabidiols XXXVIII[70] are of particular

interest. The cannabidiols bear a structural similarity to the 1,2-dihydropyridines XXXIX prepared in our studies[190].



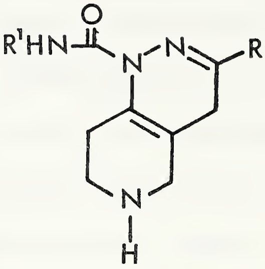
XXXIII

R = aryl
R^1 = H, Me



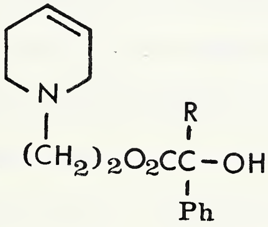
XXXIV

R, R^1, R^2 = alkyl



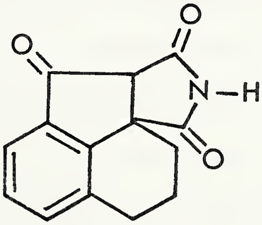
XXXV

R = alkyl, aryl, heteroaryl
R^1 = H, alkyl, aryl

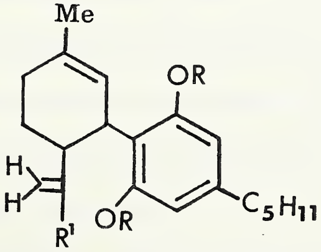


XXXVI

R = Ph, cyclohexyl

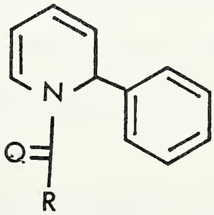


XXXVII



XXXVIII

R = H, Ac
R^1 = Me, CH_2OAc



XXXIX

	R
a	Me
b	OMe
c	OEt
d	Ph

The structural diversity of these agents has made it difficult to rationalize a universal receptor site or mechanism of action[71]. Various approaches aimed at providing a common basis for anticonvulsant properties have met with variable success. Correlation of physicochemical parameters with pharmacological activity has received much attention recently[72,73]. Equations which provide these correlations are derived via the method of least squares using a computer.

The physicochemical parameters examined include lipophilic (π)[74,75,78], electronic (σ,σ^*,F,R)[76], and steric (Es)[77] effects. These parameters have been developed in an effort to rationalize the effect of substituents on the pharmacological activity of a parent drug. Comprehensive reviews[79-84] provide a thorough treatment of this subject.

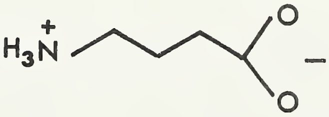
The most active exponents have been Hansch and co-workers. Their basic ρ-σ-π equation[85,86], or its modification, has enjoyed extensive use. The substituent partitioning parameter π[87-89] has been employed extensively and is defined as the difference between the logarithms of the octanol-water partition coefficients of the substituted and unsubstituted parent compound. For example, π for the NH_2 group is obtained by subtracting the logarithm of the partition coefficient for benzene (P_H) from that of aniline (Px), i.e. $\pi = \log Px - \log P_H$. The logarithm of the partition coefficient (log P) of a compound may be calculated from the log P of the parent molecule and the π value of the substituent.

Most anticonvulsants have a log P of approximately 2[72]. Such is the case for barbiturates[90] and hypnotics[91] as well as chlordiazepoxide (log P = 2.44) and diphenylhydantoin (log P = 2.47). The optimum value for antielectroshock activity is reportedly 1.75[92].

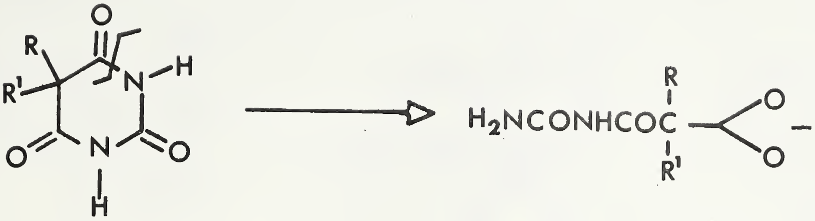
Departure in either direction from this 'ideal' value results in more specific activity. The tranquillizer chlorpromazine and the sedative meprobamate have log P values of 5.35 and 0.71 respectively.

However, reliance on log P values is an oversimplification since minor structural modifications have been shown to change activity from anticonvulsant to stimulant in nature[93]. The epileptogenic effect of some drugs[95-97] has been associated with the amide group, a feature common to many anticonvulsants. Although this anticonvulsant to stimulant conversion has been recognized, evidence suggests that log P values alone give good correlation with anticonvulsant properties[92]. Correlation with the steric parameter Es indicates that a bulky substituent at the N^1-position of hydantoins will reduce anticonvulsant activity[72].

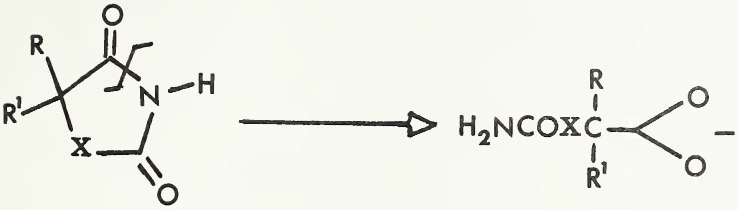
Molecular orbital calculations[94] indicate that the net atomic charge at a biologically active center or at the hydrogen bonding atoms could not be correlated with anticonvulsant activity. Similar calculations have been used to determine the preferred conformations of antiepileptic metabolites XL and XLI. The distance between the terminal nitrogen and a carboxylate oxygen was found to be approximately equal to that in gamma aminobutyric acid (GABA), a neurotransmitter[108] believed to be involved in the anticonvulsive process.



gamma aminobutyric acid



barbiturates XL



hydantoins (X = NH)
oxazolidinediones (X = O)
succinimides (X = CH_2)

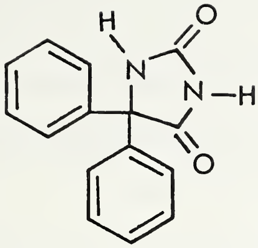
XLI

On this basis it was suggested[109] that these metabolites XL and XLI mimic GABA and are responsible in part for the antiepileptic activity. These results require qualification since the metabolites were determined in vitro while their actual levels in vivo were found to be markedly low.

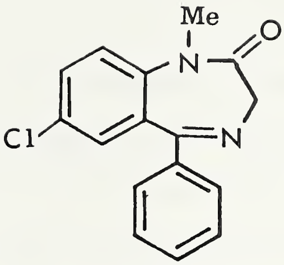
Artificial intelligence techniques[112] have been applied to the correlation of chemical structure with pharmacological activity using common basic atomic fragments for several classes of compounds including anticonvulsants[110-111].

A series of studies have attempted to associate the common anticonvulsant properties of chemically different compounds with their stereochemical similarities[98]. Examination of structures XLII-XLVI indicates the presence of two common structural features; viz:

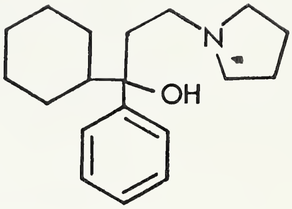
1. Two hydrophobic groups such as phenyl or cyclohexyl.
2. Two electron donating atoms, such as oxygen or nitrogen, capable of hydrogen-bonding.



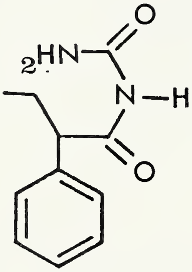
XLII



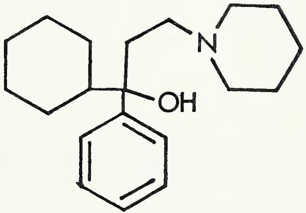
XLIII



XLIV



XLV

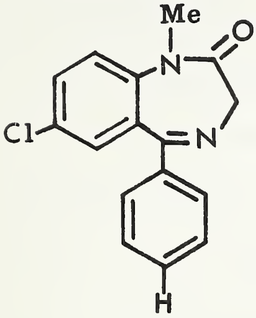


XLVI

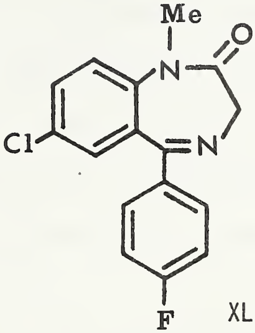
These groups have been shown to occupy similar positions in space. Thus the conformational similarities of diphenylhydantoin (XLII)[99], diazepam (XLIII)[100], procyclidine (XLIV)[101], trihexyphenidyl (XLVI}[102], and ethyl phenacemide (XLV)[104] are implicated as determinants of pharmacological activity.

This observation suggests that all of these agents act on the same type of receptor. The absence of conformational similarity[103] of sulthiame (XXVIII) to these agents implies a different mechanism of anticonvulsant action. The mechanism for sulthiame has been associated with carbonic anhydrase inhibition, a property not exhibited by the other agents. It has been suggested that the search for anti-epileptic agents should be conducted on the basis of their conformational as well as chemical similarities to existing drugs[105].

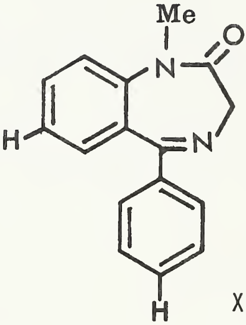
However, these conclusions were based on conformationally similar, pharmacologically active compounds. While the structures XLVII-XLIX are virtually superimposable, 4^1-fluoro (XLVIII) and 7-dechlorodiazepam (XLIX) do not exhibit the pharmacological activity of diazepam (XLVII). This observation suggests that both pharmacologically active and inactive compounds be examined prior to a correlation of conformation with activity[106].



XLVII



XLVIII



XLIX

Efforts to correlate anticonvulsant activity with inhibition of monoamine oxidase[54] and certain NAD-dependent oxidations[52,107] have been unsuccessful.

1.3.0.0.0 The Chemistry of 1,2-dihydropyridines

The resonance structures of pyridine and pyridinium salts suggest that nucleophilic attack is most facile at the 2-, 4-, or 6-positions[163]. Strong nucleophiles react preferentially at the C-2 position of pyridine while substituted pyridines often undergo C-4 substitution as well. The latter site is favored by weak nucleophiles[151]. These theoretical considerations are supported by the principle of hard and soft acids and bases[230,231] and are confirmed by experimental findings.

Organolithium reagents are strong nucleophiles and are expected to prefer α-substitution in the pyridine series thereby providing a facile route to the 1,2-dihydropyridine system.

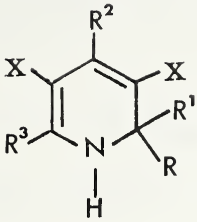
Complete reviews discussing the structure, synthesis, physical and chemical properties of 1,2-dihydropyridines up to 1971[232] and 1972[233] have appeared in the literature. N-Acylpyridinium salts have also been reviewed[157,220]. The following discussion will therefore provide a general treatment of 1,2-dihydropyridines with particular emphasis on those areas pertinent to the thesis.

1.3.1.0.0 Synthesis of 1,2-dihydropyridines

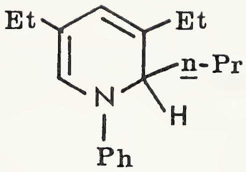
1.3.1.1.0 Synthesis of 1,2-dihydropyridines by condensation and cycloaddition reactions

The versatility of the Hantzsch synthesis provides a general route to 1,4-dihydropyridines and involves the condensation of an aldehyde with an active methylene compound and ammonia[113]. This procedure generally does not afford 1,2-dihydropyridines although they have been reported in rare cases. Thus, use of a ketone as the aldehyde component yields highly substituted 1,2-dihydropyridines L[114,115].

Note: Correct numbering of α-reduced pyridines would require that they both be 1,2-dihydropyridines. However, ambiguity may arise, particularly with unsymmetrically substituted pyridines, and therefore, for purposes of clarity, the 1,2-, 1,6-numbering convention will be followed.



L

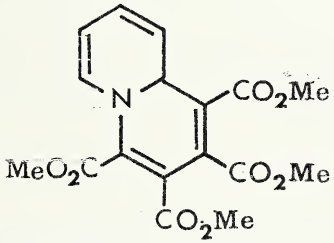


LI

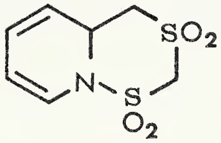
X = CN, Ac
R, R^1, R^2, R^3 = H, alkyl, aryl

Condensation of an enol ether and a β-amino nitroalkane[116] and reaction of acetone with ammonia[117] are reported to afford 1,2-dihydropyridines. The acid catalyzed product from the reaction of butanal and aniline possesses the 1,2-dihydropyridine structure LI[118].

1,2-Dihydropyridines LII and LIII are products of the cycloaddition of pyridine with the dienophiles dimethyl acetylene-



LII

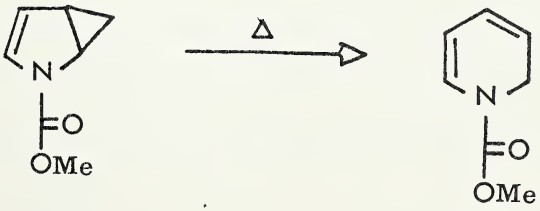


LIII

dicarboxylate[119] and sulfene[120] respectively.

1.3.1.2.0 Synthesis of 1,2-dihydropyridines from other ring systems

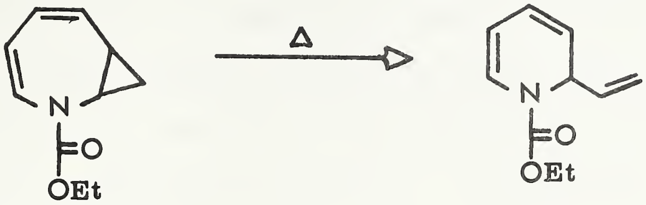
Pyrolysis of the homopyrrole LIV afforded the 1,2-dihydropyridine



LIV LV

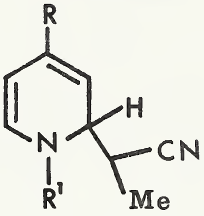
LV[121,122]. More highly substituted 1,2-dihydropyridines were similarly prepared[123].

Pyrolysis of the homoazepine derivative (LVI) gives the 1,2-dihydropyridine LVII in good yield[124]. 1,2-Dihydropyridines have also been prepared from the isomeric 1,4-dihydropyridine. In this way the 2-substituted-1,2-dihydropyridine LVIII was obtained by treatment of the isomeric 1,4-dihydropyridine with acrylonitrile[125].



LVI

LVII



R = H, trimethylsilyl

R^1 = trimethylsilyl, 2,6-dichlorobenzyl, phenyl

LVIII

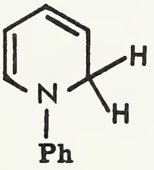
Photolysis of certain Hantzsch 1,4-dihydropyridines also yield 1,2-dihydropyridines in low yields[126].

1.3.1.3.0 Synthesis of 1,2-dihydropyridines by nucleophilic addition of metal hydrides

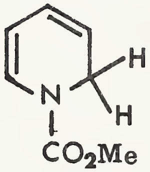
1,2-Dihydropyridines are accessible from the sodium borohydride reduction of pyridines and their salts[127], particularly those which bear electron withdrawing groups[128,130] at the 3- and/or 5-positions[132]. These preparative routes may also afford 1,4- [134] and/or 1,6-

dihydropyridines[135] and tetrahydropyridines as products[129,131,136,137]. The exact product composition is dependent on the steric[138] and electronic effects of the substituents present and also whether a protic[137,139-141] or aprotic[142] solvent is used.

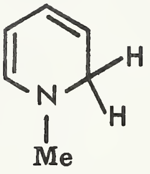
Sodium borohydride reduction of unsubstituted pyridinium salts provides a useful route to 1,2-dihydropyridines lacking a C-2 substituent. Thus reduction of N-phenylpyridinium chloride yields LIX as well as some of the 1,4-isomer[143]. The reaction of pyridine with methyl chloroformate in the presence of sodium borohydride affords N-methoxycarbonyl-1,2-dihydropyridine (LV) in which formation of the 1,4-isomer is negligible if the reaction is conducted at -70°. Treatment of LV with lithium aluminum hydride affords LX in quantitative yield[144].



LIX



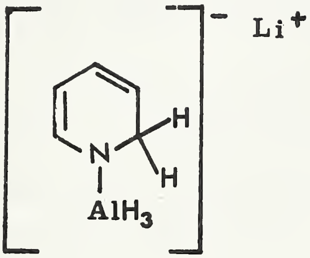
LV



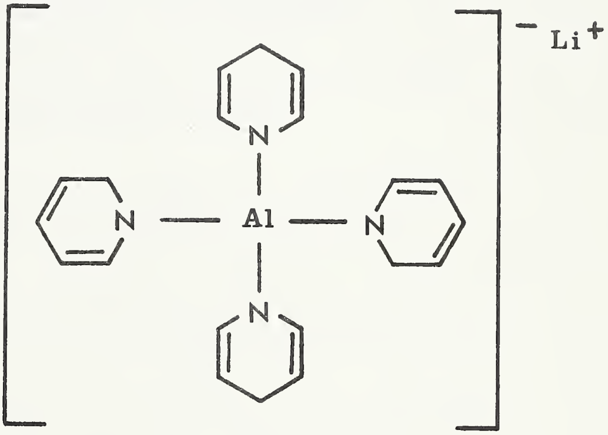
LX

Pyridines which are substituted at the 3- and 5-positions with electron withdrawing groups react with lithium aluminum hydride to give 1,2- and 1,4-dihydropyridines[133,146]. Reaction of the complex hydride $NaAlH_2(OCH_2CH_2OCH_3)_2$ with 3,5-dicyanopyridine affords only the corresponding 1,4-dihydropyridine[145]. This observation suggests that the steric effect of the bulky hydride reagent plays an important role in determining the position of hydride attack.

Pyridine reacts with lithium aluminum hydride to form an adduct originally assigned[147,148] structure LXI but which was later revised[149] to LXII. While carboxylic acids and esters were inert to LXII, certain aldehydes and ketones were readily reduced. Diaryl ketones were particularly susceptible to reduction.

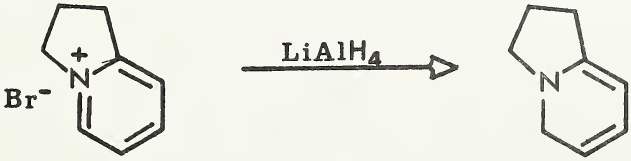


LXI



LXII

Lithium aluminum hydride reduction of the indolizinium salt LXIII affords the 1,2-dihydropyridine LXIV which served as a useful enamine for condensation with aromatic aldehydes in the synthesis of the alkaloid elaeocarpine[150].

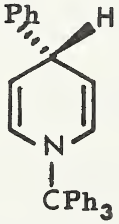


LXIII LXIV

1.3.1.4.0 Synthesis of 1,2-dihydropyridines by nucleophilic addition of organometallic reagents

Although nucleophilic addition to pyridine and its derivatives may occur at the 2-, 4- or 6-positions[151], organometallic reagents usually attack preferentially at the C-2 or C-6 position[236]. 1,2-Dihydropyridines are therefore obtained from the reaction of organometallic reagents with pyridines and pyridinium salts.

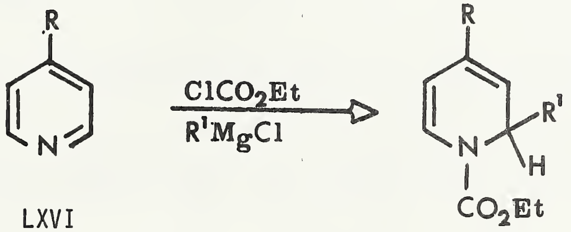
The reaction of pyridinium salts with Grignard or organocadmium reagents is much more efficient than reaction with organolithium reagents[152,153] and provides a useful synthesis of 1,2-(1,6-)-dihydropyridines. Thus reaction of N-alkyl or N-arylalkyl-3-cyanopyridinium salts with alkyl Grignard afforded 1,2-, 1,6-dihydropyridine mixtures while aryl Grignard gave only the 1,6-isomer[152]. Similar results were obtained from the reaction of organocadmium reagents with 3-carbomethoxypyridinium salts[152]. The position of substitution is influenced by the steric size of the N-substituent[154] since the reaction of phenylmagnesium bromide with N-triphenylmethylpyridinium fluoroborate affords the 4-substituted product LXV[152].



LXV

The preparation of 1,2,4-trisubstituted-1,2-dihydropyridines by the reaction of Grignard reagents with 1,4-dialkylpyridinium salts has been reported[155,156].

N-acyl-1,2-dihydropyridines are usually considerably more stable than N-alkyl or N-arylalkyl-1,2-dihydropyridines. For example, reaction of 4-alkylpyridines LXVI with ethyl chloroformate and Grignard reagent affords stable N-ethoxycarbonyl-1,2-dihydropyridines LXVII[158].

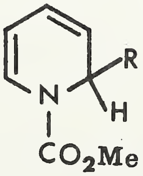


LXVI

LXVII

R = H, Me, Et, t-Bu
R^1 = n-Bu, t-Bu, Ph

Similar treatment of unsubstituted pyridines with organocuprates provides 1,4-dihydropyridines in high yield[159]. The percentage of the 1,2-isomer LXVIII formed could be minimized by conducting the reaction at low temperatures.

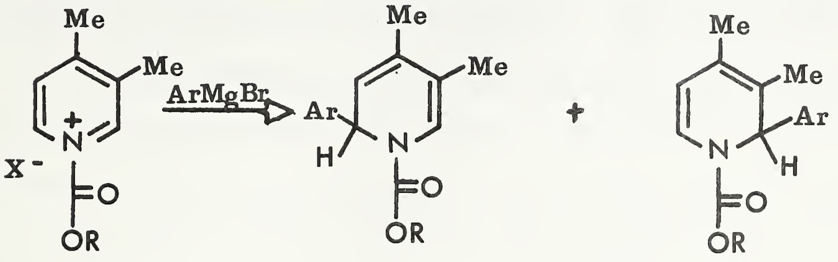


R = alkyl, aryl

LXVIII

The reaction of alkoxy (or aryloxy) carbonyl-3,4-lutidinium salts LXIX with substituted aryl Grignard reagents affords 1,2- and 1,6-

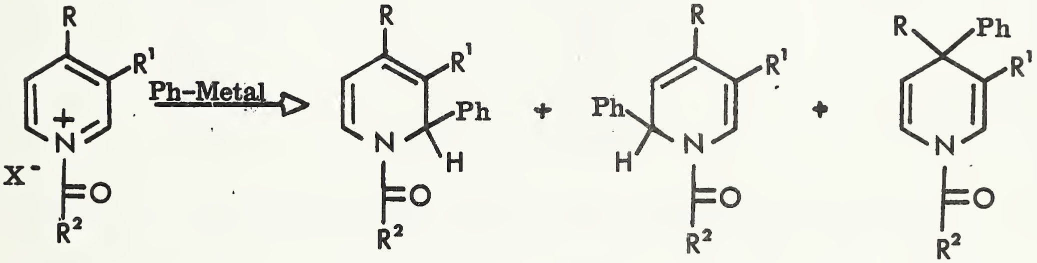
dihydropyridine mixtures (LXXI and LXX respectively)[154]. Regioselectivity (towards the less hindered 6-position) was most evident



LXIX LXX LXXI

R = alkyl, aryl

when R = phenyl and particularly when Ar = ortho-substituted phenyl. The reaction of N-acyl-3,4-disubstituted pyridinium salts LXXII with organometallic reagents other than Grignard has also been examined[153].

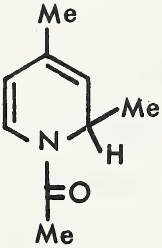


LXXII LXXIII LXXIV LXXV

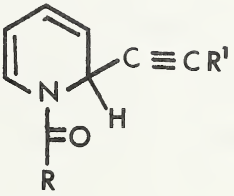
Metal = Cd, MgBr, Li
R = H, Me
R^1 = H, Me, PhCO
R^2 = Me, Ph, OEt

Thus when R' = H the expected 1,2-dihydropyridine LXXIII was isolated regardless of which organometallic reagent was used. When $R^1 = CH_3$ and R^2 = OEt both magnesium and cadmium organometallics afforded 1,2- and 1,6-dihydropyridine mixtures (LXXIII and LXXIV respectively), with the 1,6-isomer LXXIV predominant. While magnesium and cadmium

organometallic reagents are regioselective towards the 2- and 6-positions of the N-ethoxycarbonyl salt they behave quite differently towards 1,3-dibenzoylpyridinium chloride. Both reagents gave mixtures of 1,4- and 1,6-dihydropyridine (LXXV and LXXIV respectively) with the 1,3-dibenzoylpyridinium salt. However, the Grignard reaction also affords diphenyl-3-pyridylcarbinol which is the product of addition to the carbonyl carbon at the 3-position. Reaction of N-acetyl-4-picolinium chloride with methylmagnesium iodide gave the 1,2-dihydropyridine LXXVI[153]. The potent electrophilicity of N-acylpyridinium salts is illustrated by their reaction with the weakly nucleophilic silver acetylides to afford 2-alkynyl adducts LXXVII[160]. The reaction of N-acylpyridinium salts with trialkylalkynylborates proceeds regiospecifically to yield 1,4-dihydropyridines[161].



LXXVI

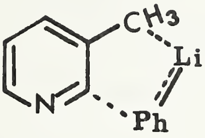


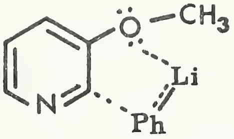
LXXVII

R = aryl
R^1 = Ph

In marked contrast to their reaction with pyridinium salts, the reaction of organolithium reagents with pyridines is a useful route to 1,2-dihydropyridines. The orientation of addition, however, parallels the observed preference for the α-positions of pyridinium salts[162]. This is particularly evident in the reaction of 3-substituted pyridines with organolithium reagents[163]. Whereas 3-alkylpyridines[164-167] afford mixtures of the 2,3- and 2,5-disubstituted aromatic products, the preponderance of the 2,3-isomer[169] has been

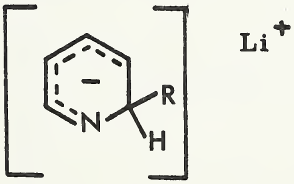
ascribed to a specific activation of the C-2 position by the 3-alkyl substituent. This is suggested as being mediated by an electron-deficient bond or by London dispersion forces[168,170]. The complex LXXVIII is similar to LXXIX which has been postulated to be responsible

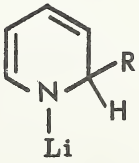

LXXVIII


LXXIX

for the singular formation of the 2,3-isomer from the reaction of 3-amino or 3-methoxypyridine with phenyllithium[171]. The orientation of this substitution has also been rationalized in terms of nucleophilic reactivity[172].

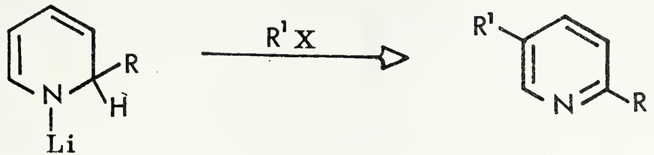
The reaction of pyridine with organolithium reagents is believed to involve formation of a sigma-complex intermediate LXXX[173], which is capable of reducing ketones[174-177]. The adduct LXII obtained from the reaction of lithium aluminum hydride and pyridine[147-149] is also a good hydride donor suitable for reduction of ketones as well as the preparation of 3-substituted pyridines[178]. Isolation[179,180] and nmr spectral characterization[162,179-181] of pyridine-organolithium adducts LXXXI provided the first unambiguous evidence for the


LXXX


LXXXI

	R
a	Me
b	n-Bu
c	Ph

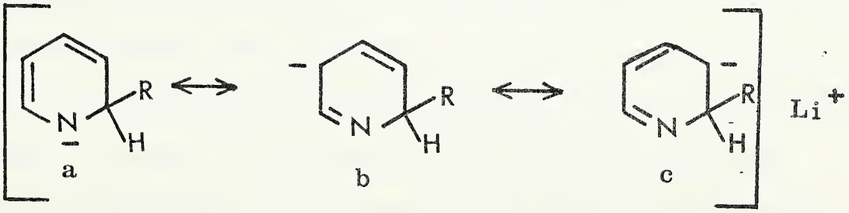
existence of LXXXI. Quinolines have since been shown to give similar adducts with organolithium reagents[182-184]. Reaction of adducts LXXXI with electrophilic reagents has been utilized for the synthesis of 2,5-disubstituted pyridines LXXXII[177]. In this way direct beta-alkylation[185,186], arylation[185], arylalkylation[185,187], hydroxy-alkylation[187], aminoalkylation[187], thiation[188], amination[186], sulfonation[186], bromination[185-186], selenation[186], and dimerization[186] were easily effected.



LXXXI

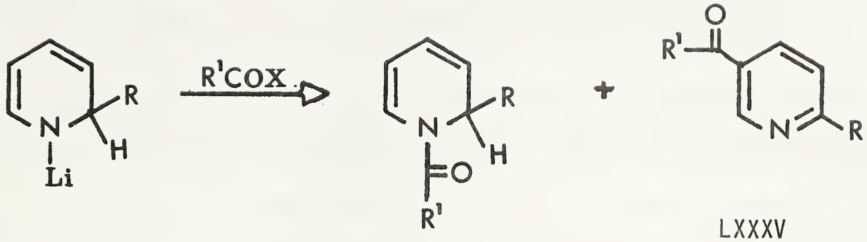
LXXXII

The mesomeric structures LXXXIII a-c suggest that reaction with electrophiles should afford both N- and C-substituted products. Reaction of LXXXI with esters, anhydrides and acid chlorides gave rise to 2-substituted-5-acylpyridines LXXXV and N-acyl-1,2-dihydro-pyridines LXXXIV[189]. The ratio of nitrogen to carbon acylation products was dependent upon the strength of the electrophile[189,190].



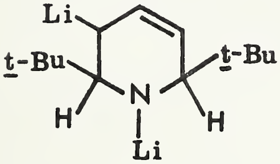
LXXXIII

Treatment of pyridine with excess organolithium reagent affords products arising from nucleophilic addition at the gamma- and/or both alpha-positions[191]. 1,5-Dilithio-2,6-di-tertiary-butyl-1,2,5,6-

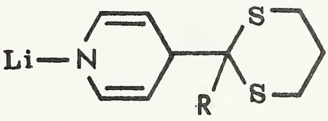


LXXXI LXXXIV LXXXV

tetrahydropyridine (LXXXVI) was shown to be an intermediate in the preparation of 2,6-disubstituted pyridines[180].



LXXXVI



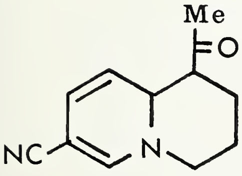
LXXXVII

Reaction of lithiated 1,3-dithianes with pyridine provide 4-substituted pyridines via the 1,4-intermediate LXXXVII[192]. Reaction of pyridine-1-oxides with organometallic reagents generally yield deoxy or ring opened products rather than the expected 1,2-dihydropyridines. Treatment of pyridine-1-oxide with phenylmagnesium bromide[194] affords the acyclic compound III rather than N-hydroxy-2-phenyl-1,2-dihydropyridine (II)[26]. Phenyllithium appears to react in a similar fashion[193].

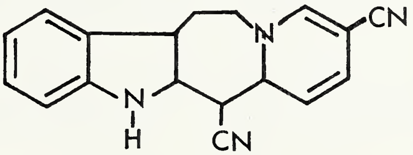
1.3.1.5.0 Miscellaneous syntheses of 1,2-dihydropyridines

Reaction of pyridinium salts with sodium dithionite, sodium hydrazide, alkoxides, or metals generally give 1,4-dihydropyridines[232]. Reaction with active methylene compounds also afford 1,4-derivatives[195,196], although 1,2-dihydropyridines have been reported[196,197].

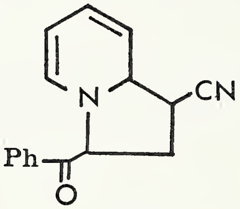
Bicyclic 1,2-dihydropyridines LXXXVIII[198], LXXXIX[199], and XC[200], have been prepared via base catalyzed cyclization to the pyridinium ring.



LXXXVIII

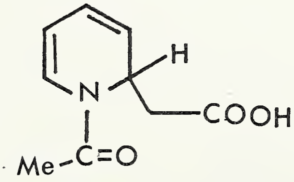


LXXXIX



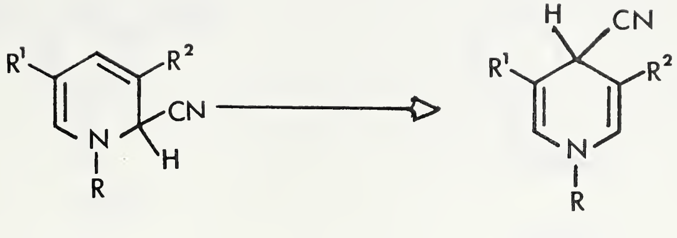
XC

Treatment of pyridine with acetic anhydride in the presence of a niacytin hydrolysate affords the unstable product XCI[201].



XCI

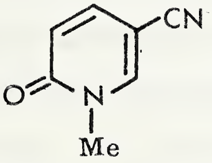
The addition of cyanide ion to pyridinium salts[162] yields the kinetically favored 2-cyano-1,2-dihydropyridine XCII which undergoes rearrangement to the thermodynamically more stable 4-cyano isomer XCIII[202,203]. Reaction of pyridinium salts with nucleophiles usually give rise to products of kinetic control.



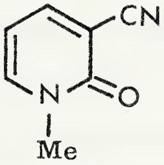
XCII XCIII

R = Me, benzyl, 2,6-dichlorobenzyl
R^1 = CH$_3$, Cl, CO$_2$Et, PhCO, MeCO
R^2 = H, CN, Cl, Br

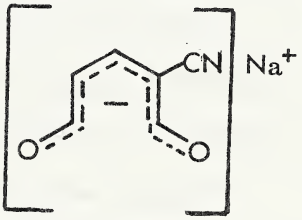
The action of hydroxide ion on pyridinium salts generally yield unstable products[204] although 2-hydroxy-1,2-dihydropyridines have been isolated[202]. The formation of a mixture of 1,2-, 1,4-, and 1,6-dihydropyridines in addition to the two isomeric 2-pyridones XCIV and XCV has recently been reported[206]. The glutaconaldehyde derivative XCVI resulting from ring-opening was also obtained.



XCIV



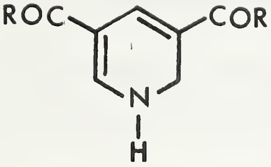
XCV



XCVI

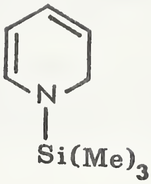
Thiation[196] and amination[196,205] of the alpha and/or gamma positions of 3-substituted pyridinium salts was found to be dependent on the nature of the 3-substituent. In situ nmr characterization of the adducts was performed since reversibility of nucleophilic addition reaction did not permit product isolation.

Controlled catalytic hydrogenation of 3,5-disubstituted pyridines yields 1,2-dihydropyridines XCVII[207,208], while treatment of pyridine with trimethylsilane and palladium affords a complex mixture containing the dihydropyridine XCVIII[209].



XCVII

R = Me, OEt, OMe



XCVIII

1.3.2.0.0 Physical properties of 1,2-dihydropyridines

1.3.2.1.0 Electronic structure of 1,2-dihydropyridines

Molecular orbital calculations indicate that the nitrogen lone pair and the electrons of the two olefinic bonds are localized. However substantial delocalization occurs when 3- and/or 5-electron-withdrawing substituents are present. Nmr studies on the adduct obtained from reaction of pyridine with n-butyllithium suggest[181] that 20% of the negative charge is located at the 3- and 5-positions and the remainder is associated with nitrogen or the nitrogen-lithium bond.

1.3.2.2.0 Ultraviolet absorption spectra of 1,2-dihydropyridines

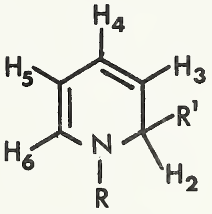
1,2-Dihydropyridines generally absorb at longer wavelengths (> 350 nm) than 1,4-dihydropyridines (300 nm) due to the dienamine system of the former. The exact position and intensity of the λ max is dependent upon the nature of the substituents, especially electron withdrawing substituents at the 3- and/or 5-positions[232,233].

1.3.2.3.0 Infrared spectra of 1,2-dihydropyridines

The dienamine system of 1,2-dihydropyridines exhibit two stretching vibrations of medium to strong intensity which appear in the 1520-1640 cm^{-1} region[209,232,233].

1.3.2.4.0 Proton magnetic resonance spectra of 1,2-dihydropyridines

The chemical shifts, which usually appear in the range 4.2-6.75, and multiplicity of the signals are dependent on the nature of the ring substitution pattern. The low to high field positions for the protons of 1,2-disubstituted-1,2-dihydropyridines IC are generally[179,190] $H_6 > H_4 > H_3 > H_5 > H_2$. The H_2 position varies and may be located between H_6 and H_4 when the C-2 substituent is aryl. Typical J values (Hz) are $J_{2,3} = 4$; $J_{3,4} = 8$; $J_{4,5} = 5.5$; and $J_{5,6} = 6$.



IC

R = acyl, acyloxy
R^1 = alkyl, aryl

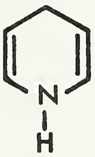
1.3.2.5.0 Mass spectra of 1,2-dihydropyridines

The major fragmentation of 1,2-disubstituted-1,2-dihydropyridines[247] involves expulsion of the C-2 substituent as a radical. Minor pathways include loss of the N-substituent and ring fragmentation.

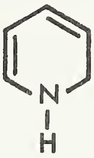
1.3.3.0.0 Chemical properties of 1,2-dihydropyridines

1.3.3.1.0 Stability of 1,2-dihydropyridines

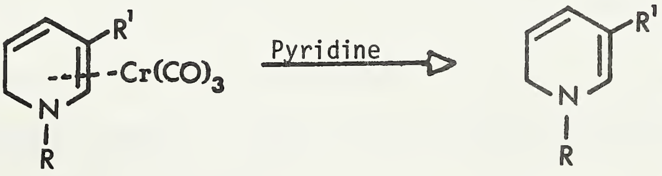
High molecular weight dihydropyridines are generally more stable than their low molecular weight counterparts. Thus highly substituted or polycyclic[198,199] dihydropyridines are usually isolable. Stability is further enhanced if substituents at the 1-, 3-, and/or 5-positions are electron-withdrawing groups and are capable of resonance interaction. The ensuing conjugation serves to reduce the nucleophilicity of the dienamine system. This is apparent from the observed stability of N-acyl[189] or phenyl[143] vs N-alkyl-1,2-dihydropyridines[213]. Recent studies[210] indicate that N-methyl-1,4-dihydropyridine is more stable than the 1,2-isomer. The parent 1,4-dihydropyridine (C) is remarkably stable[144]. 1,2-Dihydropyridine (CI) has not been isolated. Unstable dihydropyridines CIII may be conveniently handled as the stable[211,212]



C



CI



CII

CIII

R, R^1 = alkyl

carbonylchromium complexes CII from which they are easily recovered as shown above[213].

1.3.3.2.0 Oxidation of 1,2-dihydropyridines

1,2-Dihydropyridines may be oxidized by dehydrogenation[154], hydride transfer[174-175], or disproportionation[207] to the corresponding pyridine compound.

1.3.3.3.0 Reduction of 1,2-dihydropyridines

Catalytic reduction with palladium-charcoal and hydrogen gas afford tetrahydro- or hexahydropyridines whereas reduction using metal hydrides gives rise to tetrahydropyridines[137,141].

1.3.3.4.0 Nucleophilic addition to 1,2-dihydropyridines

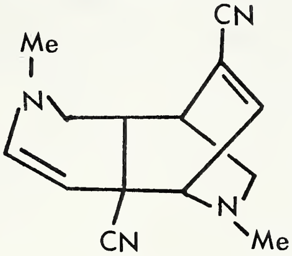
The enamine system of 1,2-dihydropyridines is sufficiently electron rich to undergo reaction with electrophiles at the beta-position[186,214,215]. Nucleophilic addition of cyanide ion to the C_6-position of a 1,2-dihydropyridine has been reported[216,217].

1.3.3.5.0 Cycloaddition reactions of 1,2-dihydropyridines

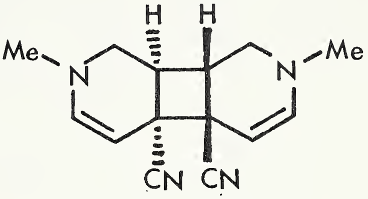
The use of 1,2-dihydropyridines as dienes complements their behaviour as enamines. Reaction with suitable dienophiles provides [2 + 2] and [4 + 2] cycloadducts.

Sodium borohydride reduction of N-methyl-4-cyanopyridinium iodide in strongly alkaline solution affords the corresponding

1,2-dihydropyridine which dimerizes to the [2 + 2] CV and [4 + 2] CIV cycloadducts[218,219]. N-methyl-2-cyano-1,6-dihydropyridine forms similar adducts[135] in which the initially formed [2 + 2] product may be thermally isomerized to the [4 + 2] adduct.

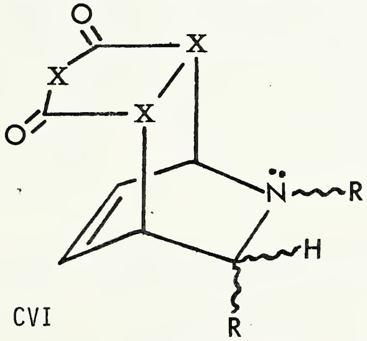


CIV

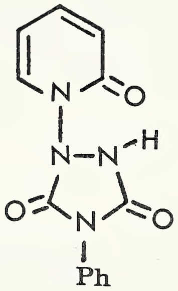


CV

1,2-Dihydropyridines are reported to undergo [4 + 2] cycloadditions with a variety of dienophiles having a fixed cis-stereochemistry. Thus adducts of type CVI have been obtained from reaction of maleic anhydride[118,144,160], maleimides[138,143,221],



CVI



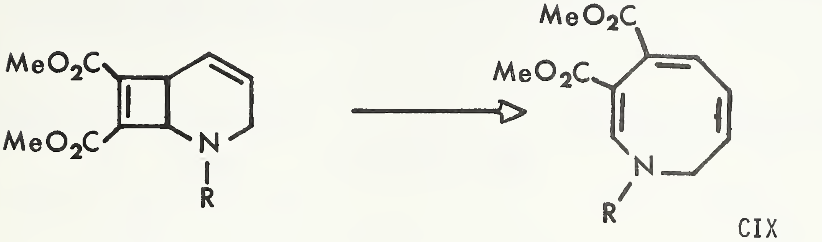
CVII

triazolindiones [221,222], and pyrazolindiones [221] with 1,2-dihydropyridines.

Substituted 2-pyridones undergo similar [4 + 2] cycloadditions[223,224] although 2-pyridone itself affords only the 1,2-addition product CVII[224] with triazolindiones.

Diels-Alder adducts have also been prepared using non-cyclic dienophiles[31,225]. Reaction of N-substituted-1,2-dihydropyridines with

acetylenedicarboxylates affords 1,2-dihydroazocines CIX[226-228] in good yield via the [2 + 2] cyclobutene intermediate CVIII.



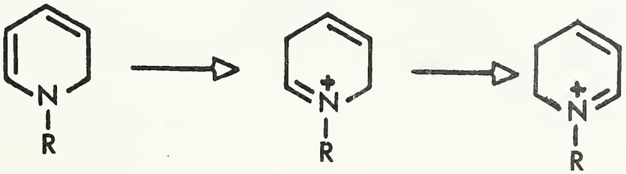
CVIII

CIX

R = alkyl, aryl, arylalkyl

1.3.3.6.0 Acid-base properties of 1,2-dihydropyridines

1,2-Dihydropyridines CX are protonated at C-5 to afford the iminium salt CXI [139] which may isomerize to CXII[217].



R = alkyl

CX

CXI

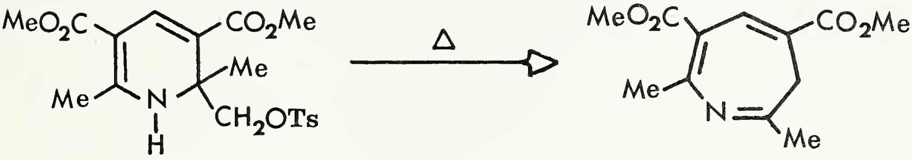
CXII

1.3.3.7.0 Isomerization of 1,2-dihydropyridines

2-Cyano-1,2-dihydropyridines prepared by addition of cyanide ion to pyridinium salts are known to isomerize to the thermodynamically more stable 1,4-isomer[203]. N-methyl and N-trimethylsilyl-1,2-dihydropyridine isomerize to the 1,4-dihydropyridine in the presence of strong base[210] or an active metal[209]. Isomerization of 1,4-dihydropyridines to 1,2-dihydropyridines is also effected using carbonylmetal complexes[211].

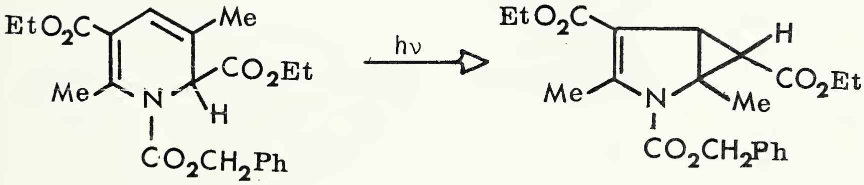
1.3.3.8.0 Rearrangements and photochemistry of 1,2-dihydropyridines

Ring expansion of the 1,2-dihydropyridine CXIII to the (3*H*)-azepine CXIV has been reported[229].

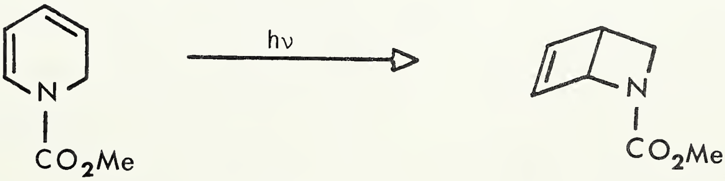


CXIII CXIV

Photolysis of CXV[123] and *N*-methoxycarbonyl-1,2-dihydropyridine (LV)[144] afford the bicyclic derivatives CXVI and CXVII respectively.



CXV CXVI



LV CXVII

2.0.0.0.0 Objectives of research

The versatility of organolithium-pyridine adducts[179,180] as reagents for the synthesis of 1,2-dihydropyridines[189,190] and β-substituted pyridines[185-187] has been clearly established.

In view of the pharmacological importance of β-substituted pyridines[36] it was desirable to extend this study to include reaction with isocyanates and pyridyl esters.

It was also of interest to examine the reactivity of N-acyl-1,2-dihydropyridines with particular attention devoted to the N-acyl-substituent and the dienamine system. This was deemed important since the amide and carbamate moieties have been implicated in structure-activity relationships of anticonvulsants. Furthermore, [4 + 2] cycloadditions of these dihydropyridines with suitable dienophiles would afford novel bicyclic compounds which incorporate a ureide functionality, a feature common to many anticonvulsants.

Finally, it was considered desirable to determine the pharmacological implications of elaboration of pharmacologically active compounds containing a fused pyridine ring system. This was to be realized in the reaction of pyridodiazepines[234] and pyridobenzothiazines[235] with organolithium reagents. The products thus formed might then exhibit pharmacological activity themselves or act as pro-drugs[37].

3.0.0.0 Discussion

All anticonvulsant agents which are in current clinical use in Canada and the United States possess the -CONH- group as a common structural feature. Thus the -CONH- unit is present in the structures of barbiturates XVI, pyrimidinediones XVII, hydantoins XVIII, acyl ureas XIX, oxazolidinediones XX, succinimides XXI, glutarimides XXII, benzodiazepines XXV, and dibenzazepines XXVI. The -SO_2NH- unit is a requirement for the anticonvulsant activity of the sulfonamides XXVII and XXVIII. Certain tetrahydropyridinediones XXXIV and tetrahydropyridines XXXVI have also been shown to possess anticonvulsant activity. The facile synthesis of N-acyl[189] and N-sulfonyl-1,2-dihydropyridines[243] provides an attractive route to compounds in which an amide or sulfonamide unit is incorporated as part of a cyclic diene system. Dienamines LXXXIV and CXIX would then be promising candidates for pharmacological evaluation as anticonvulsant agents (see Scheme I).

3.1.0.0.0 Synthesis of N-carbonyl-2-alkyl-1,2-dihydropyridines

The highly reactive and versatile intermediate, N-lithio-2-phenyl-1,2-dihydropyridine (LXXXI, R = Ph) was recently isolated[179] from the reaction of phenyllithium with pyridine. Reaction of adduct LXXXI (R = Ph) with electrophilic reagents[189,190] was subsequently utilized in the synthesis of N-substituted-2-phenyl-1,2-dihydropyridines[189,190] and 2,5-disubstituted pyridines[185,187,189,190].

The mesomeric structures LXXXIII a-c (R = Ph) suggest that electrophilic attack may occur either at carbon or nitrogen or both. The ratio

of N/C-substitution appears to be dependent on the relative electrophilicity of the acylation reagent. The ratio of N/C-substitution[189,190] dropped significantly in going from the less reactive acetyl chloride (20:1) to the more reactive benzoyl chloride (3:1) and then to the most reactive trifluoroacetyl chloride (1:16). In view of these results it was considered of interest to react other organolithium-pyridine adducts LXXXIa and LXXXIb with electrophilic reagents to determine the effect of other 2-substituents upon the site of further substitution (see Scheme I).

3.1.1.0.0 Preparation of N-lithio-2-alkyl-1,2-dihydropyridines

N-lithio-2-*n*-butyl-1,2-dihydropyridine (LXXXIb) was prepared by the dropwise addition of pyridine to an ethereal solution of *n*-butyllithium precooled to 0°C. The resulting reddish-brown solution of LXXXIb was stirred at 0° for 1 hr and then a 2 ml aliquot was titrated[237] with 0.1 N hydrochloric acid. Titration indicated that the reaction of pyridine with *n*-butyllithium afforded LXXXIb in virtually quantitative yield. Although N-lithio-2-phenyl-1,2-dihydropyridine (LXXXI, R = Ph) may be obtained as a yellow crystalline solid[190], LXXXIb precipitates as a yellow amorphous solid which was more difficult to isolate. N-lithio-2-*n*-butyl-1,2-dihydropyridine (LXXXIb) was reacted *in situ* without further purification.

N-lithio-2-methyl-1,2-dihydropyridine (LXXXIa) was similarly prepared and reacted *in situ* with the electrophile of interest.

3.1.2.0.0 Reaction of N-lithio-2-alkyl-1,2-dihydropyridines with methyl chloroformate

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) with methyl chloroformate at -77° afforded the N-substituted product LXXXIVb, the N- and C-disubstituted product CXIXb and 2-butylpyridine (CXXIb). Quantitation by Vpc analysis (see Table II) indicates that N-substituted-1,2-dihydropyridine LXXXIVb was present to the extent of 43% while the amount of 1,5-disubstituted-1,2-dihydropyridine CXIXb was only 25%. Purification of the crude reaction mixture by means of column chromatography on neutral alumina resulted in a marked decrease in the amount of LXXXIVb recovered while the amount of CXIXb remained essentially unchanged. This lower isolated yield of LXXXIVb is perhaps an indication of its instability during the purification process. The yield of N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) from the reaction of acetyl chloride with N-lithio-2-phenyl-1,2-dihydropyridine (LXXXI, R = Ph) was improved by the addition of an excess of acetyl chloride[190]. An attempt to similarly improve the yield of N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIVb) was unsuccessful. The use of five equivalents of methyl chloroformate resulted in a reduction of the yield of LXXXIVb to 35% while that of the 1,5-disubstituted product CXIXb was increased to 34%.

Vpc analysis of the reaction mixture obtained from reaction of N-lithio-2-methyl-1,2-dihydropyridine (LXXXIa) with methyl chloroformate affords N-substituted product LXXXIVa (7%), the N- and C-disubstituted product CXIXa (10%), and 2-methylpyridine (CXXIa) (7.3%). Purification of the crude reaction mixture by silica gel column chromatography gave

SCHEME I

Reaction of N-Lithio-2-alkyl-1,2-dihydropyridines with Electrophilic Reagents

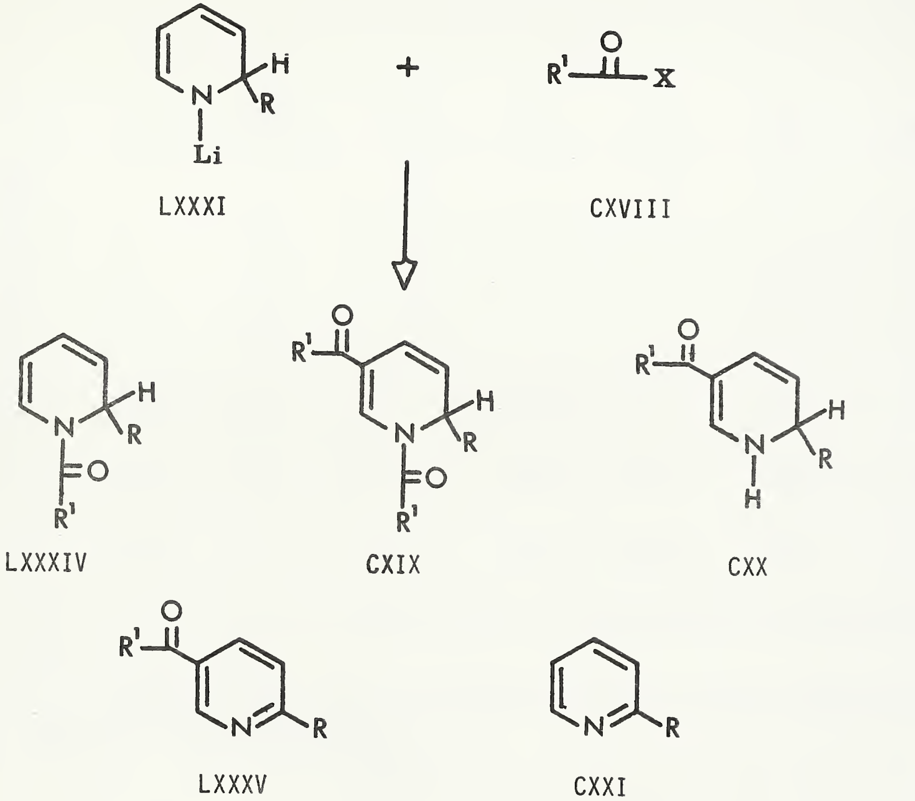
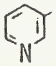
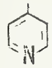
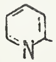


TABLE II

Percent Yield of Products from Reaction of Electrophilic Reagents with N-Lithio-2-alkyl-1,2-dihydropyridines

	R	R^1	X	LXXXIV	CXIX	CXX	LXXXV	CXXI	Comment
(a)	Me	MeO	Cl	7	10	-	-	7.3	1
(b)	*n*-Bu	MeO	Cl	43	25	-	-	5	1
(b)	*n*-Bu	MeO	Cl	35	34	-	-	6	2
(b)	*n*-Bu	MeO	Cl	15.3	33	-	-	-	3
(c)	*n*-Bu		OEt	-	-	39.6	2.7	8	4
(d)	*n*-Bu		OMe	-	-	47.4	8.6	4.8	4
(e)	*n*-Bu		OEt	-	-	47.5	4.0	15.1	4

1. Yield obtained from Vpc analysis.
2. Five equivalents of acylating reagent were used and the yield obtained from Vpc analysis.
3. Yield obtained from column chromatography.
4. Yield obtained from thin layer chromatography.

N-methoxycarbonyl-2-methyl-1,2-dihydropyridine (LXXXIVa) as a light yellow oil which darkened quickly on standing. The 1,5-disubstituted product CXIXa was not eluted.

The chemical structures of LXXXIVb and CXIXb were assigned on the basis of their spectral properties. The nmr spectrum (δ) of LXXXIVb exhibited a one H doublet ($J_{5,6}$ = 7.5) at 6.72 due to the C_6-H. The C_4-H absorption consisted of a one H doublet ($J_{3,4}$ = 8.75) of doublets ($J_{4,5}$ = 5.5) at 5.95 while the C_3-H signal appeared as a one H doublet ($J_{2,3}$ = 5) at 5.68. The one H multiplets at 5.26 and 4.75 were attributed to the C_5-H and C_2-H respectively. The methoxyl group appeared as a three H singlet at 3.78 while the n-butyl absorption was a broad nine H multiplet from 0.7 - 1.95. The ir spectrum (cm^{-1}) exhibited absorptions at 1718 (C=O) and at 1645 and 1580 (C=C) while the mass spectrum exhibited a molecular ion corresponding to $C_{11}H_{17}NO_2$: Mass calculated, 195.1259; found, 195.1266. These assignments are consistent with the structure N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIVb).

The nmr spectrum (δ) of CXIXb exhibited a one H singlet at 7.92 assigned to the C_6-H. The C_4-H absorption consisted of a one H doublet ($J_{3,4}$ = 9.75) at 6.46 while the C_3-H signal appeared as a one H doublet ($J_{3,4}$ = 9.75) of doublets ($J_{2,3}$ = 5.5) of doublets ($J_{3,6}$ = 1) at 5.62. The one H broad doublet ($J_{2,3}$ = 5.5) at 4.78 was assigned to the C_2-H. The two methoxyl three H singlets appeared at 3.86 and 3.78 while the n-butyl absorption appeared as a broad nine H multiplet from 0.65 - 1.65. The ir spectrum (cm^{-1}) exhibited peaks at 1734 and 1712 (C=O) and at 1642 and 1590 (C=C) while the mass spectrum exhibited a molecular ion corresponding to $C_{13}H_{19}NO_4$: Mass calculated, 253.1314;

found, 253.1310. These assignments are consistent with the structure 1,5-dimethoxycarbonyl-2-n-butyl-1,2-dihydropyridine (CXIXb).

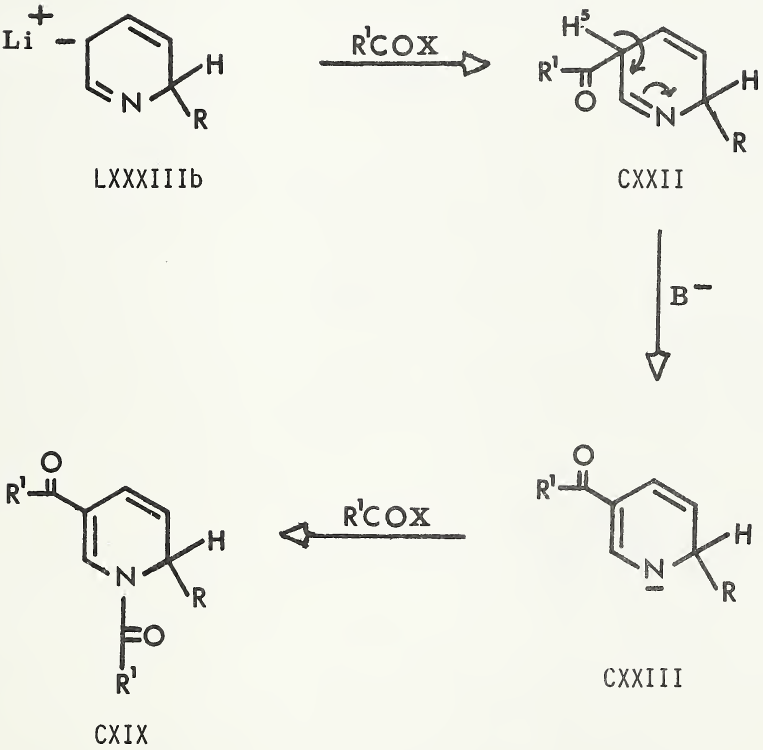
The structures of LXXXIVa and CXIXa were also assigned on the basis of their spectral properties, whereas the structures of CXXIa and b were confirmed by comparison (ir, nmr) with authentic samples.

The formation of 1,5-disubstituted-2-alkyl-1,2-dihydropyridines CXIXa and CXIXb is not unique to reactions of N-lithio-2-alkyl-1,2-dihydropyridines LXXXIa and b since the preparation of 1,5-di-(p-ethoxybenzoyl)-2-phenyl-1,2-dihydropyridine from the reaction of LXXXI (R = Ph) with p-ethoxybenzoyl chloride has been reported[190].

Two possible pathways for the formation of CXIX are shown in Scheme II and Scheme III. The mechanism proposed in Scheme II involves reaction of the acylating reagent CXVIII with LXXXIIIb to give the 2,5-dihydropyridine intermediate CXXII. Abstraction of the active C_5-H by base such as 2-alkyl- or arylpyridine CXXI (some of which is always obtained) could give rise to CXXIII which on further reaction with the acylating reagent could yield the disubstituted product CXIX. Alternatively reaction of LXXXIV with acylating reagent CXVIII to form the iminium species CXXIV which in the presence of base CXXI could also give CXIX (Scheme III). However this mechanism appears doubtful since treatment of N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIVb) with methyl chloroformate and then 2-butylpyridine (CXXIb) failed to yield disubstituted product CXIXb.

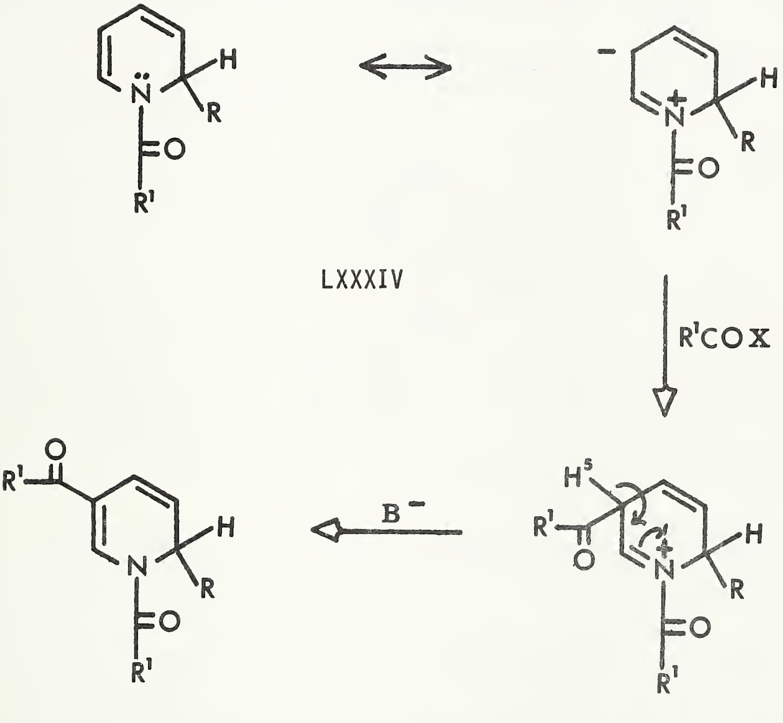
Scheme II

Possible Mechanisms for the Formation of
1,5-Disubstituted-1,2-dihydropyridines



Scheme III

Possible Mechanisms for the Formation of
1,5-Disubstituted-1,2-dihydropyridines



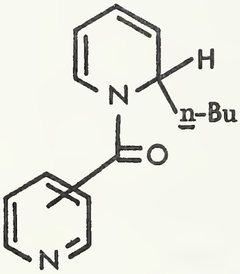
LXXXIV

CXIX

CXXIV

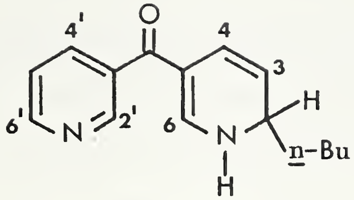
3.2.0.0.0 Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with pyridyl esters

It has been shown[189,190] that the reaction of organolithium-pyridine adducts LXXXI (R = Ph, Me, n-Bu) with acid chlorides and esters results in almost exclusive N-substitution. It was expected that reaction of LXXXIb with pyridyl esters CXVIIIc, d, and e would afford the N-substituted-1,2-dihydropyridines LXXXIVc, d, and e respectively which would be valuable synthetic medicinal intermediates for further elaboration.

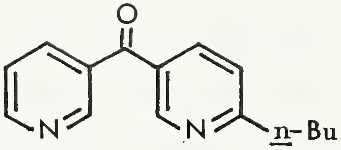


LXXXIVc-e

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) with 3-ethoxycarbonylpyridine (CXVIIIc) afforded CXXc, LXXXVc and CXXIc in 39.6%, 2.7%, and 8% yield respectively. The chemical structures of CXXc and LXXXVc were assigned on the basis of their spectral properties. The nmr spectrum (δ) of CXXc exhibited a one H doublet ($J_{2',4'} = 2$) at 8.58 assigned to the $C_{2'}$-H. The $C_{6'}$-H absorption consisted of a one H doublet ($J_{5',6'} = 5$) of doublets ($J_{4',6'} = 2$) at 8.53 while the $C_{4'}$-H signal appeared as a one H doublet ($J_{4',5'} = 8.5$) of doublets ($J_{4',6'} = 2$) of doublets ($J_{2',4'} = 2$) at 7.72. The three H multiplet at 6.94 - 7.4 was attributed to



CXXc



LXXXVc

the $C_5{}^1$-H,C_6-H, and the NH which exchanges with deuterium oxide. The one H doublet ($J_{3,4}$ = 10) at 6.54 and the one H doublet ($J_{3,4}$ = 10) at 5.15 were assigned to the C_4-H and C_3-H respectively. The C_2-H appeared as a one H multiplet at 4.29 while the broad nine H multiplet at 0.66 - 1.77 δ was assigned to the n-butyl group. The signal at 5.15 attributed to the C_3-H appeared as a sharp doublet ($J_{3,4}$ = 10) of doublets ($J_{2,3}$ = 3.5) after deuterium oxide exchange, suggesting that long range coupling with the N-H is occurring. The absorption assigned to the C_2-H at 4.29 also sharpened somewhat after deuterium oxide exchange. The ir spectrum (cm^{-1}) exhibited absorptions at 3260 (NH), 1652 (C=O) and 1580 (C=C) while the mass spectrum displayed a molecular ion corresponding to $C_{15}H_{18}N_2O$: Mass calculated, 242.1415; found, 242.1414. These assignments are consistent with the structure 2-n-butyl-5-(3'-pyridylcarbonyl)-1,2-dihydropyridine (CXXc).

The nmr spectrum (δ) of LXXXVc exhibited a three H multiplet at 8.7 - 9.05 attributed to the C_2'-H, C_6'-H, and C_6-H. The two H multiplet at 7.92 - 8.24 was attributed to the C_4'-H and C_4-H while the two H multiplet at 7.2 - 7.59 is due to the C_5'-H and C_3-H. The

two H triplet at 2.89 is due to the α-methylene of the 2-n-butyl substituent while the seven H multiplet at 0.73 - 2.17 is assigned to the remaining hydrogens of the n-butyl group. The ir spectrum (cm^{-1}) exhibited an absorption at 1670 (C=O) while the mass spectrum displayed a molecular ion corresponding to $C_{15}H_{16}N_2O$: Mass calculated, 240.1259; found, 240.1257. These assignments are consistent with the structure 2-n-butyl-5-(3'-pyridylcarbonyl)-pyridine (LXXXVc).

A bright yellow deuterochloroform solution of CXXc on standing gradually becomes lighter in intensity. Since 2-alkyl-1,2-dihydropyridines LXXXIV generally darkened on standing at room temperature the nmr spectrum of CXXc was determined over a period of time to see whether any changes had occurred. The sample of CXXc was left in the nmr tube and the spectrum was obtained at intervals over a one week time interval. Those signals corresponding to LXXXVc began to appear in the nmr spectrum and by the end of one week CXXc was completely aromatized to LXXXVc. Bubbling a stream of air through a solution of CXXc in chloroform was found to accelerate its conversion to LXXXVc. It is uncertain as to whether LXXXVc is a legitimate reaction product or whether it arises from CXXc during the purification process. The 1,2-dihydropyridines CXXc, d, and e are not products peculiar to the reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) with electrophilic reagents. 2-Phenyl-5-trifluoroacetyl-1,2-dihydropyridine CXX (R = Ph, R^1 = CF_3) was isolated as a stable solid from the reaction of LXXXI (R = Ph) with trifluoroacetyl chloride[189]. Similarly reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) with 4-methoxycarbonylpyridine (CXVIIId) afforded 2-n-butyl-5-(4'-

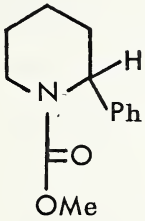
pyridylcarbonyl)-1,2-dihydropyridine (CXXd), 2-n-butyl-5-(4'-pyridylcarbonyl)-pyridine (LXXXVd) and 2-butylpyridine (CXXId) in 47.4%, 8.6% and 4.8% yields respectively (see Table II). The reaction of LXXXIb with 2-ethoxycarbonylpyridine (CXVIIIe) afforded CXXe, LXXXVe and 2-butylpyridine (CXXIe) in 47.5%, 4% and 15.1% yields respectively.

N-substituted- or 1,5-disubstituted-1,2-dihydropyridines were not detected in any of these reactions. It is expected that treatment of CXX with a non-nucleophilic base such as sodium hydride or lithium diisopropylamide followed by reaction with suitable electrophiles will afford 1,2-dihydropyridines CXIX. From these results, and those reported previously[185-187,189,190], it is evident that the reaction of organolithium-pyridine intermediates LXXXI (R = Ph, Me, n-Bu) with electrophiles allows the preparation of a variety of N- and/or C-substituted 1,2-dihydropyridines. The relative stability and facile purification of these products are features which contribute to the overall attractiveness of this synthetic method.

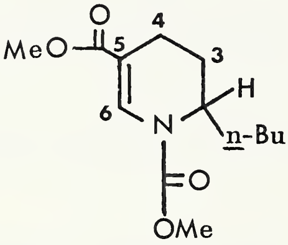
3.3.0.0.0 Catalytic hydrogenation of 1,2-dihydropyridines

Catalytic hydrogenation of N-substituted-1,2-dihydropyridines LXXXIV and CXIX with 10% palladium-charcoal and hydrogen gas provides a facile preparation of N-substituted piperidines and 1,2,3,4-tetrahydropyridines respectively in high yield. This procedure constitutes a useful synthetic method for the preparation of pharmacologically active piperidines[36,269] and tetrahydropyridines[36,269] since we have developed synthetic procedures for the preparation of 1,2-dihydropyridines with varied functionality at nitrogen and varied positions on the ring[189,190].

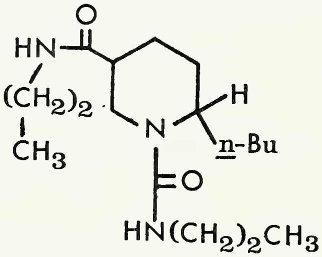
N-Methoxycarbonyl-2-phenylpiperidine (CXXV) was obtained in virtually quantitative yield by subjecting N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) to 10% palladium-charcoal and hydrogen gas for 6 hr. The nmr spectrum (δ) of CXXV exhibited a five H multiplet at 6.95 - 7.42 due to the phenyl substituent and a one H multiplet attributed to the C_2-H at 5.45. The methoxyl absorption appeared as a three H singlet at 3.69 while the remaining methylene ring hydrogens appeared as a broad eight H multiplet at 1.16 - 3.32. The ir spectrum (cm^{-1}) exhibited an absorption at 1700 (C=O) while the mass spectrum exhibited a molecular ion corresponding to $C_{13}H_{17}NO_2$: Mass calculated, 219.1259; found, 219.1263. These assignments are consistent with the structure N-methoxycarbonyl-2-phenylpiperidine (CXXV).



CXXV



CXXVI



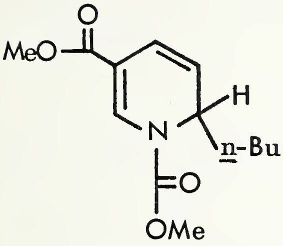
CXXVII

On the other hand catalytic hydrogenation of 1,5-dimethoxycarbonyl-2-n-butyl-1,2-dihydropyridine (CXIXb) using 10% palladium-charcoal and hydrogen gas for 3 hr did not afford the expected 1,5-dimethoxycarbonyl-2-n-butylpiperidine. The nmr spectrum of the unpurified reduction product indicated the presence of only CXXVI. Purification by thin layer chromatography on silica gel gave CXXVI in 50.3% isolated yield. The nmr spectrum (δ) of CXXVI exhibited a

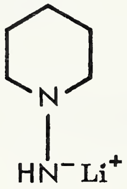
one H singlet at 7.97 assigned to the C_6-H and a one H multiplet at 4.23 attributed to the C_2-H. The three H singlets at 3.7 and 3.8 are due to the two methoxyl groups whereas the two ring methylene groups and the n-butyl substituent appear as a broad thirteen H multiplet at 0.67 - 1.6. The ir spectrum (cm^{-1}) exhibited absorptions at 1730 and 1708 (C=O) and at 1640 (C=C) while the mass spectrum gave a molecular ion corresponding to $C_{13}H_{21}NO_4$: Mass calculated, 255.1465; found, 255.1471. These assignments are consistent with the structure 1,5-dimethoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridine (CXXVI).

Since the 3,4-olefinic bond of CXIXb is disubstituted it is expected to be more easily hydrogenated catalytically than the trisubstituted 5,6-double bond. Repeated efforts to reduce the 5,6-olefinic bond of CXXVI were unsuccessful. For example, treatment of CXXVI with 10% palladium-charcoal and hydrogen gas for 31 hr or with sodium borohydride in methanol resulted in recovery of starting material. 1,5-Dimethoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridine (CXXVI) was then subjected to lithium metal and n-propylamine at reflux temperature for 23 hr. The nmr spectrum (δ) of the resulting product exhibited broad absorption at 0.7 - 4.2. The disappearance of the C_6-H singlet at 7.97 suggested that the 5,6-olefinic bond had been reduced. In addition the two singlets due to the two methoxyl groups were also absent. The ir spectrum (cm^{-1}) exhibited absorptions at 3300 (NH) and 1652 (C=O). This spectral evidence suggested that the product in question was CXXVII so this problem was not examined further. In retrospect it appeared that suitable derivatization of the 1,5-substituents of CXIXb and CXXVI would afford novel bicyclic

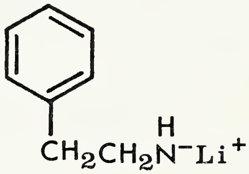
products. Nucleophilic displacement of either methoxyl group of 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (CXIXb) by reaction with a nitrogen anion was unsuccessful. Treatment of CXIXb with CXXVIII, obtained from the reaction of *N*-aminopiperidine and *n*-butyllithium, gave mainly unreacted 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (CXIXb). The reaction of *N*-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with phenethylamine or CXXIX, prepared by reaction of phenethylamine with *n*-butyllithium, afforded unreacted starting materials.



CXIXb



CXXVIII

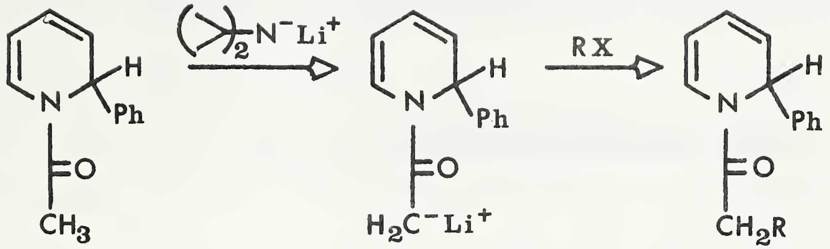


CXXIX

3.4.0.0.0 Preparation of N-acetyl-2-phenyl-1,2-dihydropyridine carbanion and subsequent reaction with iodomethane

It was expected that the active methyl group of *N*-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) on treatment with strong base would afford carbanion CXXX. Reaction of CXXX with suitable electrophiles would then afford *N*-substituted-1,2-dihydropyridines CXXXI.

The reaction of *N*-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) with lithium diisopropylamide[241] afforded CXXX which on treatment with iodomethane and purification by thin layer chromatography on silica gel gave CXXXI (R = Me) and XXXIXa in 54.3% and



XXXIXa CXXX CXXXI

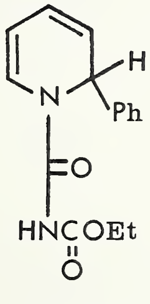
6.2% isolated yield respectively. No attempt was made to improve the yield of CXXXI (R′ = Me).

The nmr spectrum (δ) of CXXXI (R = Me) exhibited a five H multiplet at 7.28 due to the phenyl substituent. The one H doublet ($J_{5,6}$ = 7.5) at 6.49 was assigned to the C_6-H while the one H doublet ($J_{2,3}$ = 5.5) at 6.18 was attributed to the C_2-H. The one H multiplet at 5.95, 5.75 and 5.3 are attributed to the C_4-H, C_3-H and C_5-H respectively. The methylene group appeared as a two H quartet (J = 7) at 2.36 while the methyl signal was present as a three H triplet (J = 7) at 1.1. The ir spectrum (cm^{-1}) exhibited absorptions at 1678 (C=O) and at 1650 and 1583 (C=C) while the mass spectrum exhibited a molecular ion corresponding to $C_{14}H_{15}NO$: Mass calculated, 213.1154; found, 213.1152. These assignments are consistent with the structure N-propionyl-2-phenyl-1,2-dihydropyridine (CXXXI, R = Me). This procedure provides a convenient synthesis of N-acyl-1,2-dihydropyridines CXXXI which might otherwise be inaccessible. Preliminary results indicate that the carbanion CXXX is not sufficiently nucleophilic to attack the ester group of 3-methoxycarbonylpyridine.

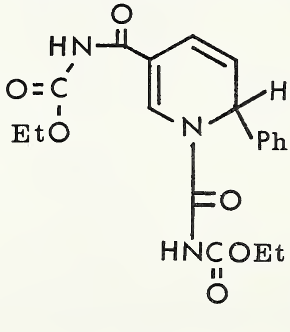
3.5.0.0.0 Reaction of N-lithio-2-substituted-1,2-dihydropyridines with isocyanates

N-Lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) reacts with ethyl isocyanate to afford N-ethylaminocarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIV, R = n-Bu, R^1 = EtNH) and 2-n-butyl-5-ethylaminocarbonylpyridine (LXXXV, R = n-Bu, R^1 = EtNH) in 33.5% and 48.4% yield respectively[270]. A similar reaction with N-lithio-2-phenyl-1,2-dihydropyridine (LXXXI, R = Ph) afforded the N-substituted product LXXXIV (R = Ph, R^1 = EtNH) in 61% yield[270] as the sole product.

Treatment of LXXXI (R = Ph) with ethoxycarbonyl isocyanate gave the N-substituted-1,2-dihydropyridine LXXXIVf and the 1,5-disubstituted 1,2-dihydropyridine CXIXf in low yield. These yields are greatly improved if 2-phenyl-1,2-dihydropyridine (CXXXIIa) is used rather than LXXXI (R = Ph). In this way LXXXIVf and CXIXb were obtained in 21.8% and 40% yield respectively[270]. The latter product is particularly interesting since the N- and C_5-substituents incorporate chemically reactive ethyl carbamate groups suitable for derivatization. It was therefore considered desirable to extend the scope of these reactions



LXXXIVf



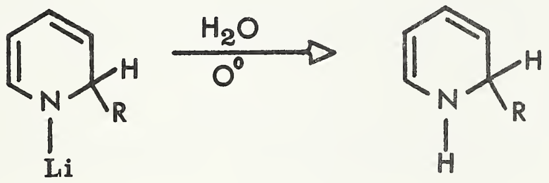
CXIXf

to include other isocyanates which would afford similar 1,2-dihydropyridines potentially capable of undergoing further derivitization.

Reaction of N-lithio-2-substituted-1,2-dihydropyridines LXXXIa and b with trichloroacetyl isocyanate^{294} afforded an intractable tar.

The reaction of γ-chloro-*n*-propyl isocyanate^{295}, prepared from tetrahydro-1,3-oxazin-2-one^{296}, with N-lithio-2-*n*-butyl-1,2-dihydropyridine (LXXXIb) also gave intractable material.

It was apparent that organolithium-pyridine adducts LXXXI were not suitable for the synthesis of the desired N- and C-substituted 1,2-dihydropyridines structurally related to LXXXIV and CXIX. The reaction of 2-alkyl(aryl)-1,2-dihydropyridines CXXXIIa and b with trichloroacetyl isocyanate and γ-chloro-*n*-propyl isocyanate was subsequently investigated.



a, R = Ph
b, R = *n*-Bu

LXXXI

CXXXII

Careful hydrolysis of an ethereal solution of LXXXI affords a light yellow solution of CXXXII. The lithium hydroxide which is formed adheres to the sides of the reaction vessel as a white solid and the solution of CXXXII may then be removed using a syringe. The reaction of trichloroacetyl isocyanate with 2-phenyl-1,2-dihydropyridine (CXXXIIa) gave intractable tar as did the reaction of γ-chloro-*n*-propyl isocyanate with 2-*n*-butyl-1,2-dihydropyridine

(CXXXIIb). It is now apparent[297] that approximately 10% of the lithium hydroxide remains in solution which is then transferred along with the 2-alkyl(aryl)-1,2-dihydropyridine CXXXII. Acyl isocyanates are known to polymerize rapidly in the presence of basic catalysts[298] and it is suspected that the lithium hydroxide is perhaps acting in this capacity. Furthermore, the ability of acyl isocyanates to undergo 1,2- and 1,4-cycloadditions[299] may make reaction across the olefinic bonds of LXXXI and CXXXII more attractive than N- or C-substitution.

3.6.0.0.0 The Diels-Alder reaction of N-substituted-1,2-dihydropyridines with dienophiles

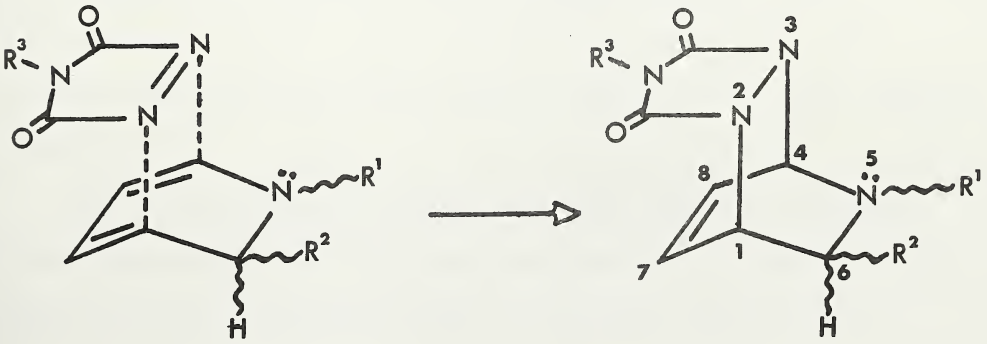
The five-membered heterocyclic ring and -CONH- unit are common structural features of the hydantoins XVIII, oxazolidinediones XX, succinimides XXI and the potent anticonvulsant XXXVII. The diene component of 1,2-dihydropyridines is known to react with five-membered heterocyclic dienophiles such as maleic anhydride[118,144,160] and N-phenylmaleimide[138,143] to afford Diels-Alder cycloaddition ($\pi 2 + \pi 4$) products. The adducts formed from the cycloaddition reaction of these dienophiles with N-acyl and N-sulfonyl-1,2-dihydropyridines would possess a five-membered heterocyclic ring and a tetrahydropyridine ring incorporating an N-acyl or N-sulfonyl substituent. The $\pi 2 + \pi 4$ cycloaddition reaction presents a unique opportunity to examine the stereochemistry as well as the anticonvulsant activity of the bridged cycloadducts formed from the reaction of 1,2-dihydropyridines with certain dienophiles.

3.6.1.0.0 Diels-Alder reaction of N-substituted-1,2-dihydropyridines with 1,2,4-triazoline-3,5-diones

The reaction of N-acyl- and N-sulfonyl-1,2-dihydropyridines with 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa) were investigated initially in view of the report that CXXXVIIIa is one of the most reactive dienophiles known[248].

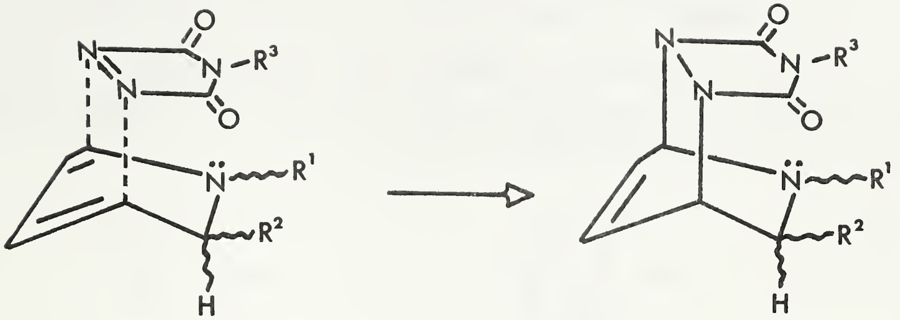
Addition of substituted 1,2-dihydropyridines to a bright red solution of 1,2,4-triazoline-3,5-dione CXXXVIII results in immediate discharge of the red color. Evaporation of the solvent *in vacuo* affords the cycloaddition product generally in quantitative yield. While *endo*-and/or *exo*-addition of the dienophile is possible these reactions were found to proceed stereospecifically to afford the *endo*-cycloaddition product (see Scheme IV and Table III).

Illustrations CXXXIII and CXXXIV depict the two possible preorientations of the addends from which the *endo*-CXXXV or *exo*-CXXXVI cycloadducts respectively are formed. Observing the concept of "maximum overlap" of unsaturation in the transition state[250] the preorientation CXXXIII would be favored over CXXXIV. Furthermore,



CXXXIII

CXXXV



CXXXIV CXXXVI

preorientation CXXXIV would involve considerable unfavorable steric interaction between the urazole ring and the R^1,R^2-substituents of the 1,2-dihydropyridine system. These bulky substituents would be even more compressed in the adduct CXXXVI than in the addends CXXXIV. The dienophile CXXXVIII is therefore expected to add stereospecifically to the less hindered face of the 1,2-dihydropyridine to afford the *endo*-adduct CXXXV in which the urazole ring and the substituents at the 5- and 6-positions are *anti*[118]. The reaction of N-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXc) with 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa) affords 5-*endo*-ethoxycarbonyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide (CXXXIXd). The stereochemistry of the substituents at the 5- and 6-positions was assigned on the basis of the nmr spectral evidence.

The π electrons of an olefinic bond, when placed in a magnetic field (such as that used in nmr spectroscopy), will circulate thereby generating their own magnetic field. This induced magnetic field

Scheme IV

Diels-Alder Reaction of N-Substituted-1,2-dihydropyridines with 1,2,4-Triazoline-3,5-diones

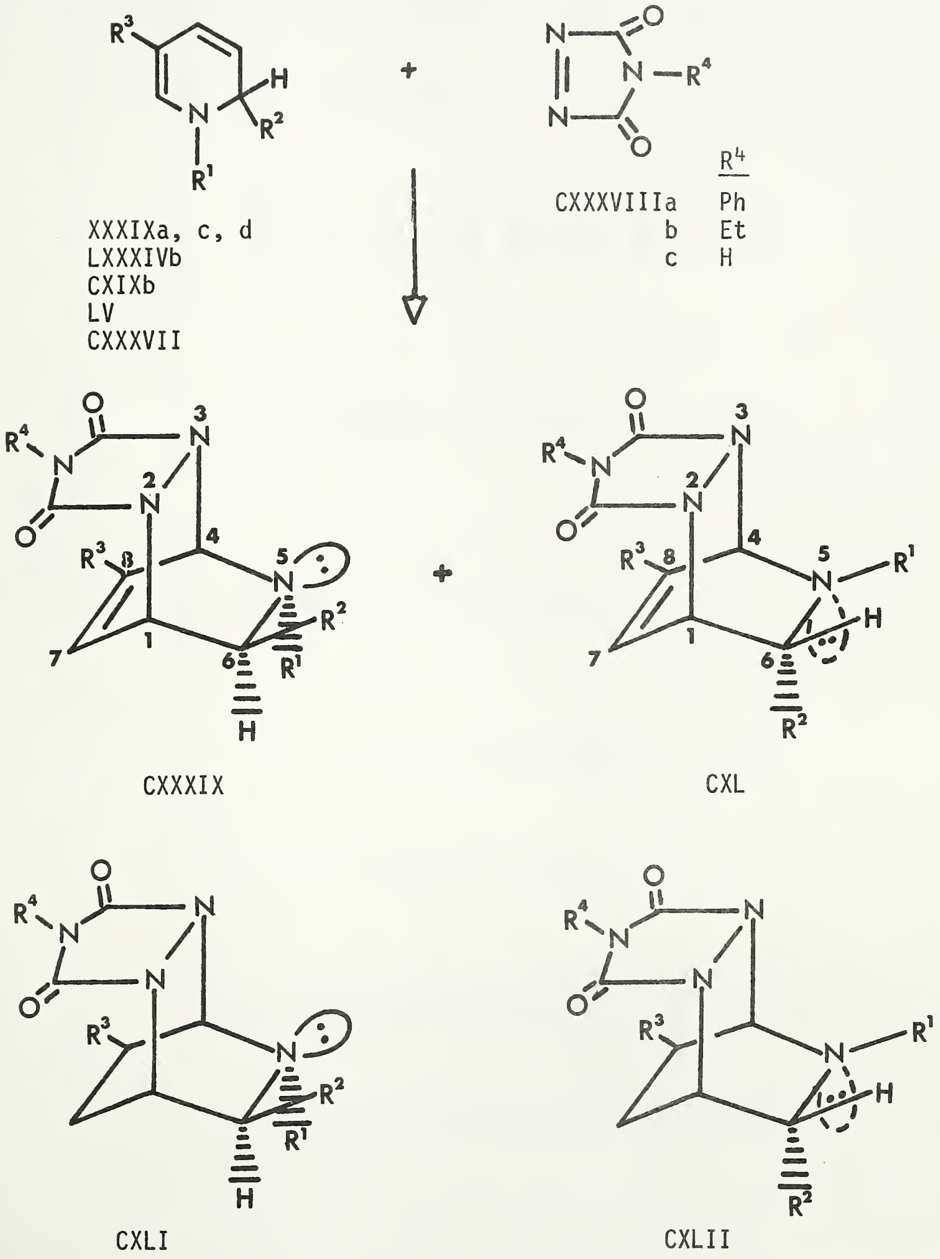
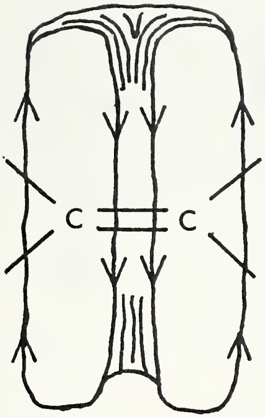


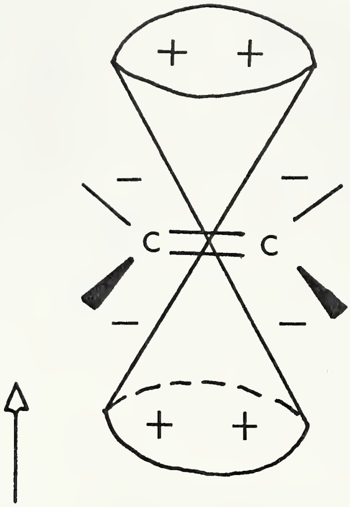
TABLE III

Reaction of N-Substituted-1,2-dihydropyridines with 1,2,4-Triazoline-3,5-diones

	XXXIXa,c,d; LXXXIVb; CXIXb; LV; CXXXVII			CXXXVIII	Temp °C	Yield of Products (%)	
	R^1	R^2	R^3	R^4		CXXXIX	CXL
(a)	COMe	Ph	H	Ph	-77	68	32
(a)	COMe	Ph	H	Ph	25	67	33
(b)	COMe	Ph	H	Et	25	69	31
(c)	COMe	Ph	H	H	o	43	26
(d)	CO_2Et	Ph	H	Ph	-77	100	-
(e)	COPh	Ph	H	Ph	25	100	-
(f)	CO_2Me	_n_-Bu	H	Ph	25	100	-
(g)	CO_2Me	_n_-Bu	CO_2Me	Ph	25	100	-
(h)	CO_2Me	H	H	Ph	25	100	-
(i)	CO_2Me	H	H	Et	-77	92	-
(j)	SO_2Me	H	H	Ph	25	100	-
(k)	SO_2Me	H	H	Et	25	89	-

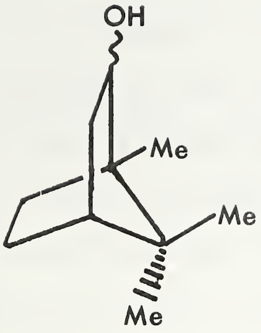


CXLIII

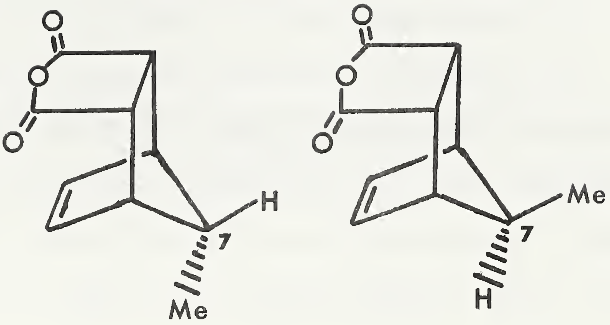


CXLIV

opposes the applied magnetic field (Ho) in the area above and below the plane of the double bond and reinforces Ho at the periphery as shown in CXLIII. This effect depends upon diamagnetic anisotropy[252] and may be best described in terms of shielding (+) and deshielding (-) zones as shown in CXLIV. Molecules which contain protons sterically oriented so that they lie in the conical zones above or below the plane (+) of an olefinic bond are shielded relative to protons located in the lateral zones (-). This effect has been observed in the Diels-Alder adducts of substituted cyclopentadienes with maleic anhydride[253]. The C-7 methyl of these adducts was found to be shielded by approximately 0.2 δ relative to the chemical shift of the corresponding methyl substituent in borneol and isoborneol (CXLV). This observation indicates that relative to the double bond the C-7 methyl has the *syn*-configuration CXLVIa rather



CXLV

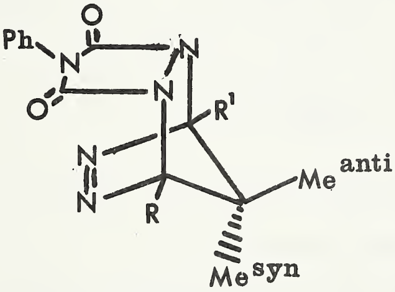


a

b

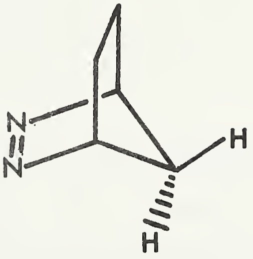
CXLVI

than the *anti*-configuration CXLVIb. A similar diamagnetic anisotropic effect for the azo linkage has been observed[251]. The Diels-Alder reaction of substituted 4,4-dimethylisopyrazoles with 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa) affords the adduct CXLVII in which



CXLVII

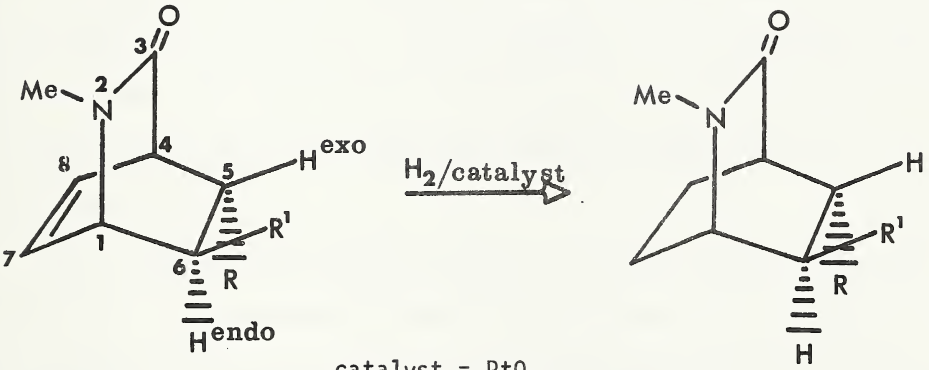
R, R^1 = Me, Ph



CXLVIII

the *syn*-methyl absorption is shielded approximately 0.8 δ compared to the *anti*-methyl absorption. The *syn*-hydrogen in CXLVIII is not significantly shielded indicating that it lies too far from the azo linkage to be affected by a diamagnetic anisotropic effect.

The diamagnetic anisotropic effects of unsaturated systems may be eliminated by such chemical means as reduction. Consequently the nmr signals for substituents which lie in the shielding zone of double bonds should experience a paramagnetic (downfield) shift upon reduction of the olefinic bond. This deshielding effect has been observed in the reduction of CXLIX to CL[254]. When $R = R^1 = CN$ the chemical shifts (δ) of the *exo*-hydrogen and *endo*-hydrogen are 3.75 and 3.37 respectively in CXLIXa and 3.75 and 3.54 respectively in CLa. This represents a downfield (deshielding) shift of 0.17 δ for the *endo*-hydrogen while the *exo*-hydrogen shift remains unchanged.



CXLIX

catalyst = PtO_2
or Pd-C

CL

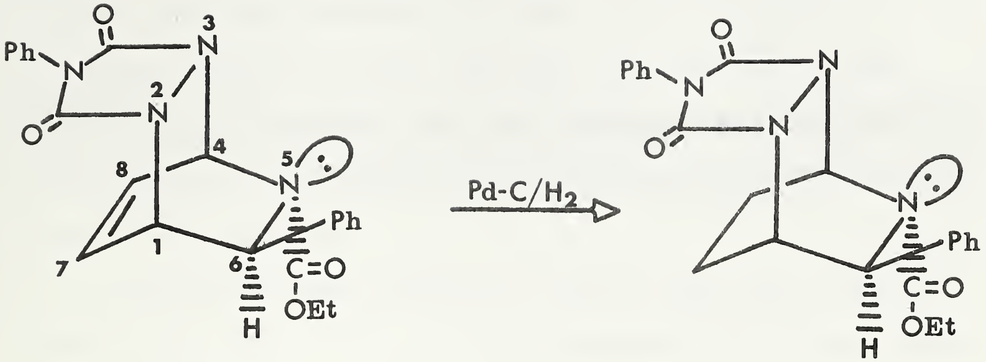
$R=R^1$

a CN
b CO_2Me

When $R = R^1 = CO_2Me$ the chemical shifts (δ) of the *exo*-hydrogen and *endo*-hydrogen are 3.76 and 3.39 respectively in CXLIXb and 3.62 and 3.46 respectively in CLb. This represents a downfield shift of 0.07 δ for the *endo*-hydrogen while the *exo*-hydrogen is shielded by 0.14 δ. Since the C-5 methoxycarbonyl substituent in CXLIXb is in

the endo-configuration it is expected that reduction of CXLIXb to CLb should cause a downfield shift for the methyl absorption. The observed chemical shifts (δ) in CXLIXb are 3.6 (endo-methyl R) and 3.65 (exo-methyl R^1) while in CLb they both appear at 3.62. This represents a downfield shift of 0.02 δ for the endo-methyl R while the exo-methyl R^1 is shielded by 0.03 δ. Although the endo-methoxycarbonyl group R is affected by the diamagnetic anisotropy of the C_7-C_8 double bond the effect is not as dramatic as that seen with the endo-hydrogen. The implication is that the methoxycarbonyl group R is sufficiently removed from the double bond to escape its full shielding effects.

The 100 MHz nmr spectrum (δ) of the cycloadduct CXXXIXd from the reaction of N-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXc) and 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa) exhibits a 10 H multiplet for the C_6- and urazole phenyl groups at 7 - 7.6. A two H multiplet at 6.74 is assigned to the C_4-H and C_8-H while a one H doublet ($J_{7,8}$ = 9.5) of doublets ($J_{1,7}$ = 5) at 6.12 is attributed to the C_7-H. The C_6-H signal appears as a one H doublet ($J_{1,6}$ = 2.5) at 5.21 and the C_1-H is a one H doublet ($J_{1,7}$ = 5) of doublets ($J_{1,6}$ = 2.5) at 5.11. The absorptions for the methylene and methyl hydrogens appear at 4.08 and 1.1 respectively. These assignments were confirmed by double resonance studies. Irradiation (δ) at 6.74 (C_4-H and C_8-H) has no effect on the C_6-H (5.21) and C_1-H (5.11) signals. Irradiation at 6.12 (C_7-H) simplifies the C_1-H signal to a doublet ($J_{1,6}$ = 2.5) while the C_6-H remains as a doublet ($J_{1,6}$ = 2.5). Irradiation of the C_6-H and C_1-H simplifies the C_7-H signal.



CXXXIXd

CXLId

The ir spectrum (cm^{-1}) exhibited bands at 1790 and 1718 (C=O) while the mass spectrum exhibited a molecular ion corresponding to $C_{22}H_{20}N_4O_4$: Mass calculated, 404.1478; found, 404.1485. These assignments are consistent with the structure 5-endo-ethoxycarbonyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXXXIXd).

The diamagnetic anisotropy of the C-7, C-8 unsaturation is expected to shield those substituents at the 5- and 6-positions which have the endo-stereochemistry. Reduction of the double bond would eliminate the anisotropy thereby deshielding the 5- and 6-substituents. Catalytic hydrogenation of CXXXIXd with 10% palladium-charcoal and hydrogen gives a product whose nmr spectrum (δ) shows a ten H multiplet for the C-6 and urazole phenyl groups at 7 - 7.6. One H multiplets at 6.43, 5.27 and 4.55 are assigned to the C_4-H, C_6-H and C_1-H respectively. The methylene hydrogens appear as a two H quartet (J = 7) at 4.15 while the methyl three H triplet (J = 7) is at 1.17. The C-7 and C-8 hydrogens are seen as a four H multiplet at 1.43 - 2.52.

The mass spectrum exhibited a molecular ion corresponding to $C_{22}H_{22}N_4O_4$: Mass calculated, 406.1641; found, 406.1629. These assignments are consistent with the structure 5-endo-ethoxycarbonyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]octane-2,3-dicarboxylic acid N-phenylimide (CXLId).

Examination of the nmr data in Table IV indicates that the chemical shift (δ) of the C_6-H is deshielded by 0.06 in the reduced compound CXLId. The methylene and methyl protons are similarly deshielded by 0.07. This indicates that the N-ethoxycarbonyl group and the C_6-H are both in the endo-configuration. It therefore follows that the C-6 phenyl must be in the exo-configuration and that the structure assigned to CXXXIXd must be 5-endo-ethoxycarbonyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-dicarboxylic acid N-phenylimide (CXXXIXd).

Reaction of N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) with 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa) gives a mixture of stereoisomers CXXXIXa (68%) and CXLa (32%). The 100 MHz nmr spectrum (δ) of the mixture exhibited an eleven H multiplet for the C-6 and urazole phenyl groups and the C_4-H from 7.05 - 7.58. The C_8-H appears as a one H doublet ($J_{7,8}$ = 8) of doublets ($J_{4,8}$ = 5.5) of doublets ($J_{1,8}$ = 1.75) at 6.82 while the one H multiplet from 6.05 - 6.5 was assigned to the C_7-H. The one H multiplet at 5.08 corresponds to the C_1-H. The spectrum also exhibits two absorptions at 5.42 and 5.16 for the C_6-H; and at 2.34 and 1.79 for the acetyl methyl group which integrated for one and three hydrogens respectively. These assignments were confirmed by double resonance studies. Irradiation (δ) at 6.82

TABLE IV

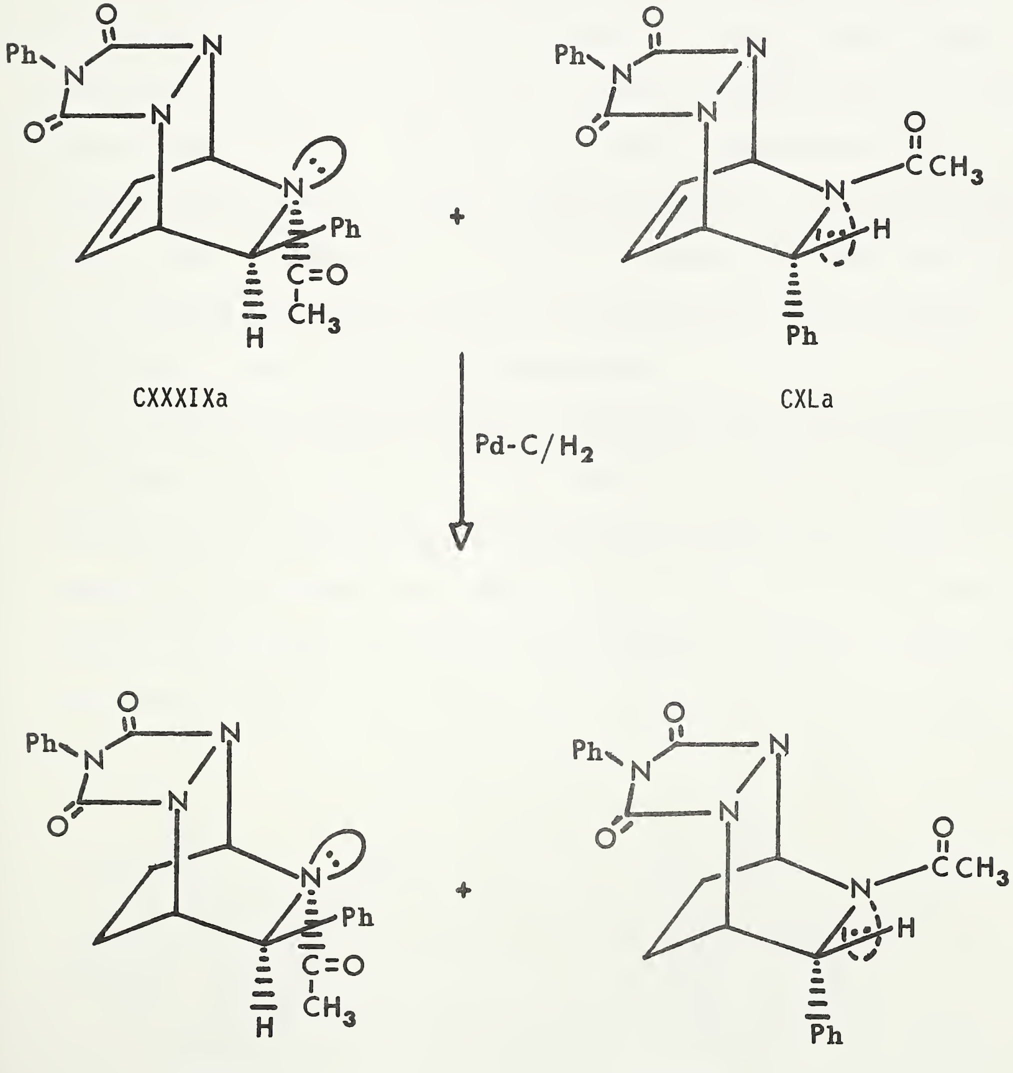
Relative Chemical Shifts (δ) of Unsaturated and Reduced Products

Compound	H_6	$H_{6'}$	$-OCH_2-$	$-CH_3$
CXXXIXd	5.21	-	4.08	1.1
CXLId	5.27	-	4.15	1.17
CXXXIXa	5.16	-	-	1.79
CXLa	5.42	-	-	2.34
CXLIa	5.4	-	-	2.36
CXLIIa	5.4	-	-	2.36

(C_8-H) has no effect on the signals attributed to the C_6-H and C_1-H. Irradiation at 5.16 (C_6-H, C_1-H) results in collapse of the C_8-H signal to a doublet ($J_{7,8}$ = 8) of doublets ($J_{4,8}$ = 5.5) while the C_7-H signal now appears as a doublet ($J_{7,8}$ = 8). The ir spectrum (cm^{-1}) shows absorptions at 1784, 1715, and 1709 (C=O) and at 1665 (C=C) while the mass spectrum exhibits a molecular ion corresponding to $C_{21}H_{18}N_4O_3$: Mass calculated, 374.1379; found, 374.1377. The diamagnetic anisotropy of the C-7, C-8 olefinic bond is expected to shield the endo-C_6-H and endo-N-acetyl methyl of CXXXIXa but to have no effect on the exo-C_6-H and exo-N-acetyl methyl of CXLa. Catalytic hydrogenation of the CXXXIXa and CXLa mixture (Scheme V) with 10% palladium-charcoal and hydrogen gas gave a mixture of the stereoisomers 5-endo-acetyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]octane-2,3-endo-dicarboxylic acid N-phenylimide (CXLIa) and 5-exo-acetyl-6-endo-phenyl-2,3,5-triazabicyclo[2.2.2]octane-2,3-endo-dicarboxylic acid N-phenylimide (CXLIIa). The 100 MHz nmr spectrum (δ) exhibits a ten H multiplet due to the C-6 and urazole phenyl groups at 7.09 - 7.77. The one H multiplets at 6.18, 5.4 and 4.62 are attributed to the C_4-H, C_6-H and C_1-H respectively. The acetyl methyl signal appears at 2.36 while the C-7 and C-8 hydrogens are displayed as a four H multiplet from 1.56 - 2.64. These assignments were confirmed by double resonance studies. Irradiation (δ) at 6.18 (C_4-H) has no effect on the C_1-H signal while irradiation at 5.4 (C_6-H) simplifies the C_1-H signal. Irradiation at 4.62 (C_1-H) simplifies the signal assigned to the C_7-H (2.64 - 1.56). The mass spectrum displayed a molecular ion corresponding to $C_{21}H_{20}N_4O_3$: Mass calculated, 376.1535; found, 376.1529.

Scheme V

Catalytic Hydrogenation of Cycloadducts from the Reaction of N-Acetyl-1,2-dihydropyridines with 1,2,4-Triazoline-3,5-diones



CXXXIXa

CXLa

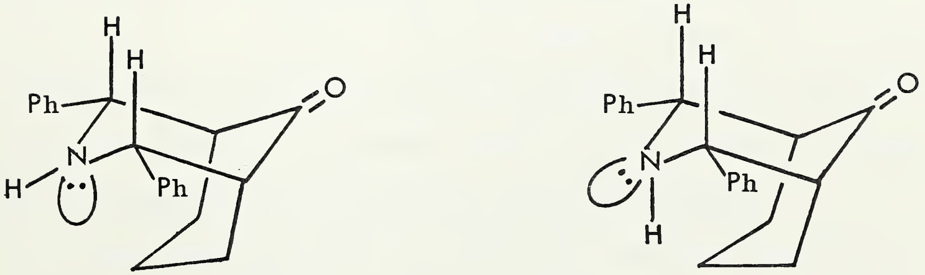
CXLIa

CXLIIa

Examination of the nmr data (δ) in Table IV indicates that after catalytic hydrogenation the endo-C_6-H of CXXXIXa at 5.16 is deshielded by 0.24 and the C-5 methyl absorption at 1.79 is deshielded by 0.57. The chemical shifts of the exo-C_6-H and C-5 methyl in CXLa remain essentially unchanged.

On the basis of these results the reaction product prior to hydrogenation must be composed of a mixture of 5-endo-acetyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXXXIXa, 68%) and 5-exo-acetyl-6-endo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXLa, 32%). Subsequent to our study[221] Krow and coworkers reported[307] the obtention of a similar mixture of stereoisomers from the cycloaddition of imines with 1,3-cyclohexadienes.

Azerbaev and coworkers recently reported[255] the separation by fractional recrystallization of two stereoisomers of 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (CLI) which were stereoisomeric with respect to the nitrogen free electron pair. The distinction between the two stereoisomers was based on the presence of Bohlmann bands in the infrared spectra of CLIa which were absent in CLIb. A necessary



a

b

CLI

requirement for obtention of these bands is the presence of an axially oriented free electron pair bearing a trans relationship with adjacent axial C-H bonds. While this requirement is fulfilled in CLIa the equatorially oriented electron pair in CLIb precludes the observance of Bohlmann bonds.

Adducts CXXXIX and CXL are also stereoisomeric with respect to the nitrogen free electron pair in which the pair is equatorial (exo) in CXXXIX and axial (endo) in CXL. In addition the two isomers differ in their stereochemistry at the C-6 position. The successful separation of CLIa from CLIb encouraged a similar separation of CXXXIXa from CXLa. Repeated efforts to resolve the two isomers by fractional recrystallization and thin layer chromatography were not successful. The isomer ratios were therefore determined from the relative nmr integrated areas for the hydrogens of the endo-and exo-N-acetyl substituent. Furthermore, the obtention of a single isomer could not be effected by varying the reaction temperature or the nature of the substituent R^4 of the triazoline dione CXXXVIII. Examination of the data in Table V indicates that the product ratio CXXXIX:CXL is relatively constant and is independent of the reaction temperature and the CXXXVIII R^4 substituent. Interconversion of the isomers CXXXIX and CXL is unlikely. Inversion about nitrogen at the 5-position is prohibited by significant ring strain while a change in the configuration of the C-6 tetrahedral carbon would necessitate cleavage of a sigma bond followed by rotation and recombination.

Furthermore, conducting the Diels-Alder reaction at different temperatures might be expected to vary the isomer ratio if CXXXIX-CXL

TABLE V

Isomeric Product Ratios for Reaction of N-Acetyl-2-phenyl-1,2-dihydropyridine

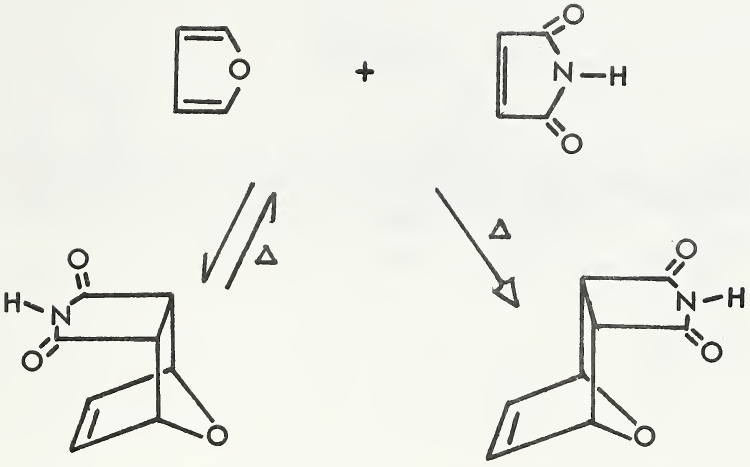
Product Mixture	Reaction Temp °C	δ CH_3 CXXXIX	δCH_3 CXL	Ratio* CXXXIX : CXL
CXXXIXa and CXLa	-77	1.79	2.34	2.1 : 1
CXXXIXa and CXLa	25	1.79	2.34	2 : 1
CXXXIXa and CXLa**	-65	1.79	2.34	1.9 : 1
	0	1.79	2.34	1.9 : 1
	+31	1.79	2.34	2.2 : 1
CXXXIXb and CXLb	25	1.78	2.3	2.2 : 1
CXXXIXc and CXLc	0	1.72	2.3	1.6 : 1

* Determined from the integration curve for the acetyl methyl hydrogens.

** Reaction was effected at -65° in an nmr tube and the spectrum was obtained at -65°, 0° and 31° respectively.

interconversion were possible. The fact that the yield of CXXXIX always exceeds that of CXL when R^1 is acetyl suggests there is less steric hindrance to the approach of CXXXVIII when the R^2 substituent is exo and R^1 is endo. The reaction of N-substituted-1,2-dihydropyridines possessing ethoxycarbonyl, methoxycarbonyl, methanesulfonyl, and benzoyl substituents at the R^1 position with CXXXVIII results in the exclusive formation of CXXXIX. The greater steric bulk of these substituents relative to an acetyl group suggests that they may exert a steric effect preventing the approach of CXXXVIII when R^2 is in the endo-and R^1 in the exo-position. It is interesting to note that a substituent (CO_2Me) occupying a central position (C_5) of the enamine system does not affect the stereochemical course of the Diels-Alder reaction. Thus the reaction of 1,5-dimethoxycarbonyl-2-n-butyl-1,2-dihydropyridine (CXIXb) with 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIa) affords CXXXIXg in quantitative yield. It has been reported[259] that N-methyl-2-pyridone substituted by a methyl group at the terminal position (C_3) of the enamine affords only the exo-adduct CLXI in the reaction with N-phenylmaleimide.

Reversible Diels-Alder reactions have been reported as illustrated by the reaction of furan with maleimide[250]. The kinetically favored endo-adduct CLII dissociates at temperatures slightly above room temperature. Recombination of the addends at the higher temperature permits the formation of the thermodynamically more stable exo-adduct CLIII. A similar endo-CXXXV to exo-adduct CXXXVI conversion without adduct dissociation could be effected by an inversion of the two bridgehead nitrogens. However, this is unlikely in the cycloadducts



CLII

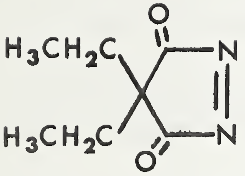
CLIII

prepared due to the extreme rigidity of the ring system. The nmr spectrum of CXXXIXd does not change at temperatures of 23°, 30°, 50° and 55° indicating that at those temperatures *endo*-*exo*-adduct conversion does not occur. The nmr spectrum of CXXXIXa and CXLa is similarly invariant over the temperature range -65° to +31° (Table V).

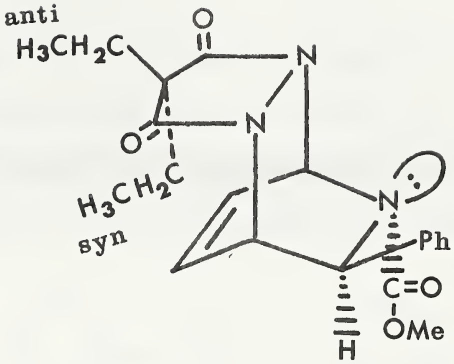
3.6.2.0.0 Diels-Alder reaction of N-substituted-1,2-dihydropyridines with 4,4-diethyl-1,2-pyrazoline-3,5-dione

The successful cycloaddition reaction of N-substituted-1,2-dihydropyridines with 1,2,4-triazoline-3,5-diones CXXXVIII prompted further investigation using other dienophiles with similar reactivity.

The reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with 4,4-diethyl-1,2-pyrazoline-3,5-dione (CLIV) affords the cycloadduct CLV in quantitative yield. The diamagnetic anisotropic effect of the C_7-C_8 double bond is evident in the nmr spectrum of CLV.



CLIV



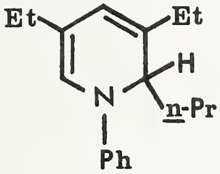
CLV

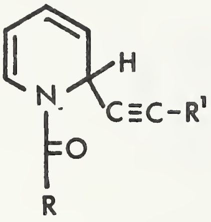
The methylene and methyl signals of the ethyl group which is syn to the C_7-C_8 double bond appear at 1.75 δ [2H, q (J=7)] and 0.79 δ [3H, t (J=7)] respectively. The ethyl group which is anti to the double bond is not influenced by the anisotropic effect since the methylene and methyl signals appear at 1.8 and 0.95 δ respectively. Adduct CLV was unstable towards column chromatography using neutral alumina and thin layer chromatography on silica gel. The adduct also decomposed on standing at room temperature, a factor which discouraged a more thorough examination of the reactivity of CLIV towards other N-substituted-1,2-dihydropyridines.

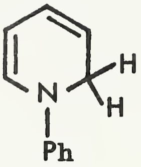
3.6.3.0.0 Diels-Alder reaction of N-substituted-1,2-dihydropyridines with maleimides

The reaction of 1-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXc) with maleic anhydride, maleimide (CLVIc) or N-phenylmaleimide (CLVIa) afforded unreacted starting material and intractable tar. For example refluxing for 48 hrs in toluene only facilitated the decomposition of the 1,2-dihydropyridine XXXIXc. Failure to form the

cycloaddition product was puzzling since N-methoxycarbonyl-1,2-dihydropyridine (LV)[144], N-phenyl-2-n-propyl-3,5-diethyl-1,2-dihydropyridine (LI)[118] and N-benzoyl-2-phenylethynyl-1,2-dihydropyridine (LXXVII, $R = R^1 = Ph$)[160] afford Diels-Alder cycloadducts


LI


LXXVII

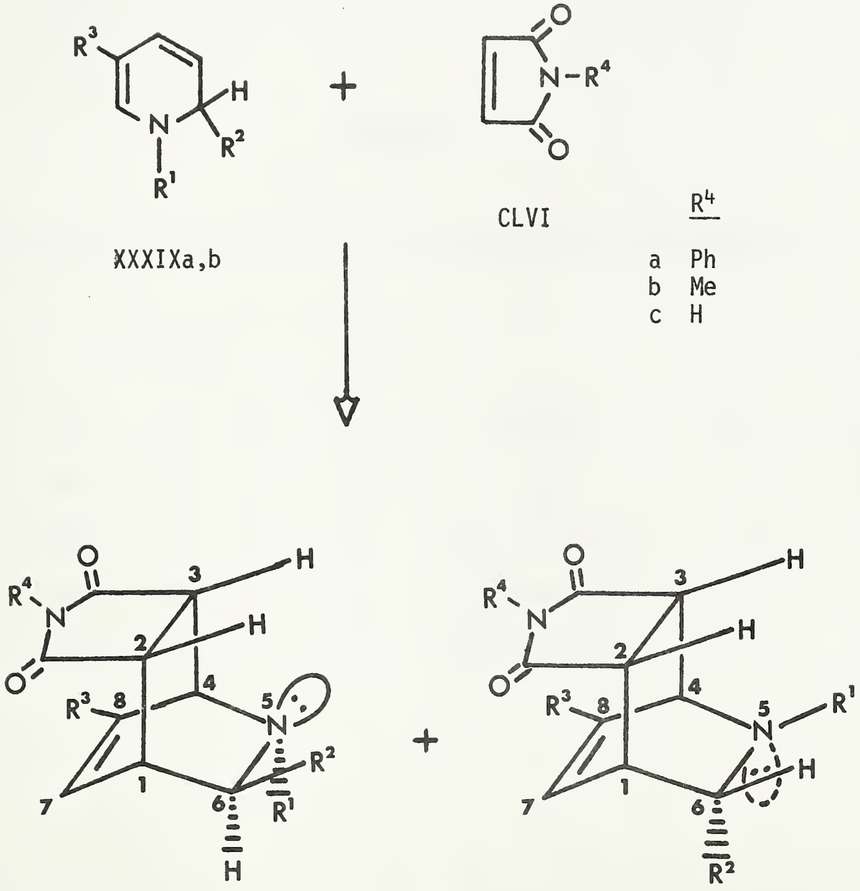

LIX

with maleic anhydride. N-phenyl-1,2-dihydropyridine (LIX)[143] did not react with maleic anhydride but did give the expected cycloaddition product with N-phenylmaleimide (CLVIa).

The reaction of N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) with N-phenylmaleimide (CLVIa) afforded CLVIIa (75%) and CLVIIIa (25%) in quantitative yield. The 220 MHz nmr spectrum (δ) of this mixture exhibited a ten H multiplet at 7.02 - 7.5 attributed to the C-6 and maleimide phenyl groups. The C_8-H appears as a one H doublet ($J_{7,8}$ = 8) of doublets ($J_{4,8}$ = 6) of doublets ($J_{1,8}$ = 1.25) at 6.61 while the two H multiplet from 5.93 - 6.14 was assigned to the C_4-H and C_7-H. The spectrum also exhibits two absorptions at 5.09 and 4.8 for the C_6-H; and at 2.3 and 1.77 for the acetyl methyl group which integrated for one and three H respectively. The one H multiplet at 3.64 was assigned to the C_1-H while the C_3-H appeared at 3.52 as a one H doublet ($J_{2,3}$ = 8) of doublets ($J_{3,4}$ = 4). The one H doublet ($J_{2,3}$ = 8) of doublets ($J_{1,2}$ = 3) at 3.34 was attributed to the C_2-H.

Scheme VI

Diels-Alder Reaction of N-substituted-1,2-dihydropyridines with Maleimides



XXXIXa,b

CLVI

	R⁴
a	Ph
b	Me
c	H

CLVII

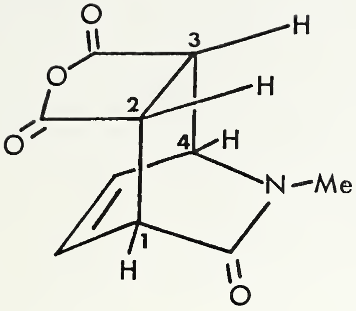
CLVIII

TABLE VI

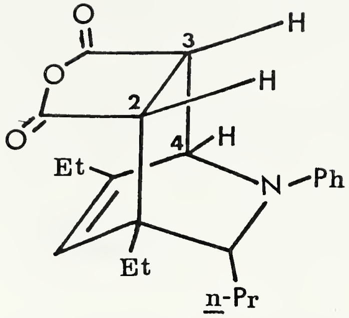
Reaction of N-Substituted-1,2-dihydropyridines with Maleimides

	XXXIXa,b			CLVI		Yield of Products	
	R^1	R^2	R^3	R^4	Catalyst	CLVII	CLVIII
(a)	COMe	Ph	H	Ph	None	75	25
(a)	COMe	Ph	H	Ph	$AlCl_3$ (5 equiv)	34	15
(b)	CO_2Me	Ph	H	Me	$AlCl_3$ (5 equiv)	56	-
(c)	CO_2Me	Ph	H	H	$AlCl_3$ (5 equiv)	52	-

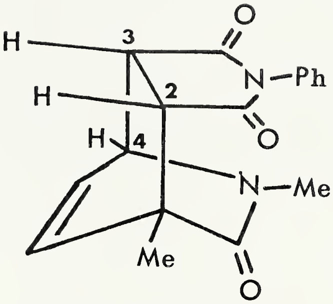
These assignments were confirmed by double resonance studies. Irradiation (δ) at 6.61 (C_8-H) has no effect on the C_6-H, C_3-H, and C_2-H signals while the signal due to the C_1-H is simplified to a doublet ($J_{1,7}$ = 5.5) of doublets ($J_{1,6}$ = 3). Irradiation of the multiplet at 5.93 - 6.14 (C_4-H, C_7-H) has no effect on the C_6-H and C_2-H signals while the C_1-H signal is simplified and the C_3-H signal appears as a doublet ($J_{2,3}$ = 8). Irradiation at 4.8 (endo-C_6-H) has no effect on the absorptions due to the C_8-H, C_4-H, C_7-H, C_3-H, C_2-H while the C_1-H signal is simplified. Irradiation at 3.64 (C_1-H) collapses the C_8-H signal to a doublet ($J_{7,8}$ = 8) of doublets ($J_{4,8}$ = 6). The multiplet assigned to the C_7-H is simplified while the C_6-H signal collapses to a sharp singlet. Irradiation at 3.52 (C_3-H) has no effect on the signals assigned to the C_8-H and C_6-H while the multiplet assigned to C_4-H and C_7-H is simplified. Irradiation at 3.34 (C_2-H) has no effect on the signals assigned to the C_8-H, C_4-H, C_7-H and C_6-H. The ir spectrum (cm^{-1}) shows absorptions at 1775 and 1710 (C=O) and at 1650 (C=C) while the mass spectrum exhibited a molecular ion corresponding to $C_{23}H_{20}N_2O_3$: Mass calculated, 372.1474; found, 372.1465. The C_7-C_8 unsaturation is expected to shield the endo-C_6-H and endo-acetyl methyl while the exo-C_6-H and acetyl methyl are unaffected. The nmr spectrum (δ) does indeed show two absorptions at 5.09 and 4.8 for the exo-and endo-C_6-H respectively and at 2.3 and 1.77 for the exo-and endo-acetyl methyl respectively. The stereochemistry of the maleimide ring in the adduct CLVII was also determined from the nmr data. It has been reported[256-260] that the stereochemistry of adducts of type CLIX-CLXVIII



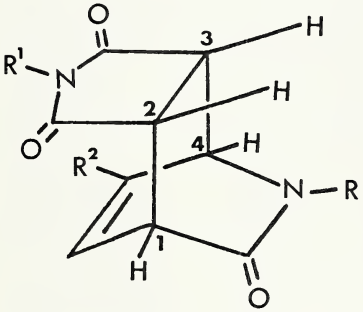
CLIX



CLX



CLXI



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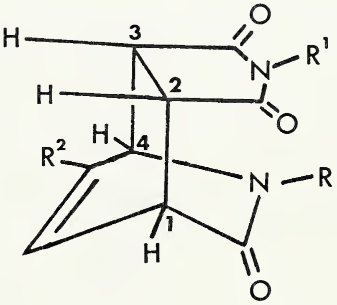


b

	R	R^1	R^2
CLXII	Me	Ph	H
CLXIII	H	Ph	H
CLXIV	n-Pr	Ph	H
CLXV	i-Bu	Ph	H
CLXVI	i-C_5H_{11}	Ph	H
CLXVII	Me	Ph	Me
CLXVIII	n-Pr	H	H

TABLE VII

Coupling Constants for the Diels-Alder Cycloadducts of 2-Pyridones with Maleic Anhydride and Maleimides

	$J_{1,2}$	$J_{3,4}$	Conformation of adduct
CLIX[256]	3.5	4	endo
CLX[118]	-	4	endo
CLXI[259]	-	2.5	exo
CLXIIa[257]	4.4	4.6	endo
CLXIIIa[258]	3.5	4	endo
CLXIIIb[258]	2.7	2.5	exo
CLXIVa[259]	4.5	4	endo
CLXVa[259]	4.5	4	endo
CLXVIa[259]	4	4	endo
CLXVIIa[259]	3.7	4	endo
CLXVIIIa[259]	4	4	endo

may be determined from the magnitude of the coupling constants for the protons at the bridgehead positions (C_1-H, C_4-H) and the adjacent protons (C_2-H, C_3-H). Examination of the data in Table VII indicates that $J_{1,2}$ and $J_{3,4}$ for exo-adduct CLXIIIb are 2.7 and 2.5 Hz respectively. Similarly exo-adduct CLXI has a $J_{3,4}$ = 2.5 Hz. On the other hand endo-adduct CLXIIIa has $J_{1,2}$ and $J_{3,4}$ of 3.5 and 4 Hz respectively. The remaining endo-adducts in Table VII have $J_{1,2}$ and $J_{3,4}$ in the range of 3.5 - 4.6 Hz. The nmr spectrum of a mixture of CLVIIa and CLVIIIa exhibited coupling constants $J_{1,2}$ = 3 Hz and $J_{3,4}$ = 4 Hz which is consistent with the endo-conformation for the maleimide ring (Scheme VI).

The anisotropic effect of the C_7-C_8 unsaturation is expected to shield the C_2-H and C_3-H of CLXIIIb but to exert no effect on the C_2-H and C_3-H of CLXIIIa. Examination of the data in Table VIII indicates that the C_2-H and C_3-H of the exo-adduct CLXIIIb are shielded by 0.37 δ and 0.05 δ respectively relative to the same protons of the endo-adduct CLXIIIa. The C_2-H and C_3-H of the exo-adduct CLXI are similarly shielded by 0.44 δ and 0.1 δ respectively relative to the endo-adduct CLXVIIa. It should also be noted that the C_1-H and C_4-H of the endo-adducts CLXIIIa and CLXVIIa are shielded relative to the same protons in the exo-adducts CLXIIIb and CLXI.

The chemical shifts (δ) for the C_2-H and C_3-H of CLX are reported[118] to be 3.1 and 3.5 respectively. The reaction of N-phenylmaleimide (CLVIa) with N-triphenylmethyl-1,2-dihydropyridine affords the endo-adduct whose nmr spectrum exhibits a multiplet at 3.1 δ assigned to the C_2-H and C_3-H. The low field position of this signal has been taken to suggest that these hydrogens are anti to the double bond and the adduct therefore has the endo-stereochemistry[138].

TABLE VIII

Chemical Shifts (δ) for the Diels-Alder Cycloadducts of 2-Pyridones with Maleimides

	H_1	H_2	H_3	H_4	Conformation of adduct
CLXIIIa[258]	4	3.52	3.7	5	endo
CLXIIIb[258]	4.15	3.15	3.65	5.15	exo
CLXVIIa[259]	3.86	3.27	3.49	4.28	endo
CLXI[259]	-	2.83	3.39	4.56	exo

The chemical shifts (δ) of the C_2-H and C_3-H of CLVIIa are 3.34 and 3.52 respectively. Although the exo-adduct was not available for comparison these chemical shift values are comparable to those observed for the endo-adducts in Table VIII and therefore substantiate the conclusions obtained from a study of the coupling constants $J_{1,2}$ and $J_{3,4}$ (Table VII). The product from the reaction of N-phenylmaleimide (CLVIa) and N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) is therefore a mixture of stereoisomers 5-endo-acetyl-6-exo-phenyl-5-azabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CLVIIa, 75%) and 5-exo-acetyl-6-endo-phenyl-5-azabicyclo[2.2.2]oct-7-ene-2,3-endo dicarboxylic acid N-phenylimide (CLVIII, 25%). Efforts to separate this mixture by fractional crystallization or thin layer chromatography were unsuccessful.

The rate of the Diels-Alder reaction is known to be accelerated by such Lewis acids as $AlCl_3$, BF_3, $SnCl_4$ and $TiCl_4$. This catalytic action is probably due to complex formation between the Lewis acid and the polar groups of the activating substituents in the dienophile[250]. It has also been suggested that the catalyst interacts with the diene as well as the dienophile[267]. Although catalysis is not expected to change the mechanism of the reaction[250] it is known that both regioselectivity[264] and endo-stereoselectivity[261,265] are increased. It was therefore of interest to determine whether addition of a Lewis acid would alter the proportion of CLVII and CLVIII formed from the reaction of N-acetyl-1,2-dihydropyridines with maleimides CLVI. Examination of the data presented in Table VI indicates that the addition of aluminum chloride did not effect the obtention of a

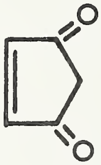
single isomer CLVII or CLVIII. A marked reduction in the recovery of CLVIIa and CLVIIIa was observed which was due to problems encountered during purification of the reaction mixture.

Since N-alkoxycarbonyl-2-phenyl-1,2-dihydropyridines had been unreactive towards maleic anhydride, maleimide (CLVIc) and N-phenylmaleimide (CLVIa) it was hoped that the addition of a catalyst would make the 1,4-cycloaddition a more favourable reaction. The reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with maleimide (CLVIc) and N-methylmaleimide (CLVIb) in the presence of five equivalents of aluminum chloride afforded the Diels-Alder adducts CLVIIc (52%) and CLVIIb (56%) respectively. The absence of CLVIIIb and CLVIIIc in these two reactions suggests that there is steric hindrance to approach of the maleimide CLVI by the exo-methoxycarbonyl substituent when the C-6 phenyl substituent is endo.

Optimum yields were obtained employing five equivalents of aluminum chloride. Boron trifluoride dietherate failed to catalyze the reaction of XXXIXa and b with maleimides CLVIb and c.

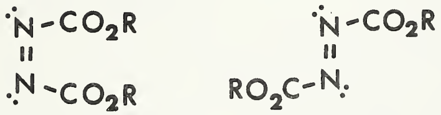
It is not surprising that maleimide (CLVIc) and N-methylmaleimide (CLVIb) require catalysis to give the Diels-Alder adduct while N-phenylmaleimide (CLVIa) does not. The reaction of electron-rich dienes with dienophiles substituted with electron withdrawing groups afford Diels-Alder adducts readily. The electron-attracting phenyl substituent of N-phenylmaleimide (CLVIa) is expected to reduce the electron density of the olefinic bond thereby increasing the reactivity of this dienophile relative to maleimide (CLVIc) or N-methylmaleimide (CLVIb).

The aluminum chloride (five equivalents) catalyzed reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with 4-cyclopentene-1,3-dione (CLXIX) afforded a dark brown solid whose nmr spectrum suggested it to be the anticipated Diels-Alder adduct. This material was unstable towards column chromatography on neutral alumina and attempts at purification by recrystallization were unsuccessful.



CLXIX

3.6.4.0.0 Diels-Alder reaction of N-substituted-1,2-dihydropyridines with acyclic dienophiles



a b

R = Et, t-Bu

CLXX

$MeO_2CC\equiv CCO_2Me$

CLXXI

Cyclic dienophiles are generally more reactive than their open chain analogs. This may be attributed to a more favorable transition-state geometry resulting from secondary orbital interaction. These secondary attractive forces[268] involve the electrons which are not

directly associated with the primary bonding process and are responsible in part for the preorientation of the addends prior to the cycloaddition reaction. One consequence of the non-cyclic state is that acyclic dienophiles may have the cis-or trans-stereochemistry. The cis-isomer CLXXa is a much more reactive dienophile than the trans-form CLXXb[262]. This may be attributed to a more efficient overlap of unsaturation in the transition state for CLXXa than for CLXXb. Furthermore, the reactivity of azodicarboxylates decrease with increasing size of the alkoxycarbonyl group[262].

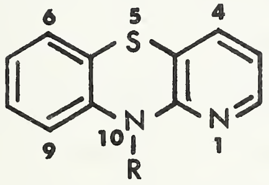
The reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with diethyl and di-t-butyl azodicarboxylate (CLXX) gave intractable tar. Since the cis-isomer CLXXa is readily converted by light into the trans-isomer[262] it may not be unreasonable to assume that the trans-isomer CLXXb is the species present[263]. This conformation may then present an unfavorable steric factor preventing the Diels-Alder reaction.

The reaction of N-substituted-1,2-dihydropyridines with dimethyl acetylenedicarboxylate (CLXXI) was investigated in view of the successful aluminum chloride catalyzed reaction of N-methoxycarbonylpyrrole with this dienophile[266]. While this study was in progress Mariano[228] and Acheson[226,227] independently reported the [2+2] cycloaddition of N-alkyl, aryl, or arylalkyl-1,2-dihydropyridines with dimethyl acetylenedicarboxylate. The resulting cyclobutene intermediate CVIII subsequently rearranged to the corresponding 1,2-dihydroazocine CIX.

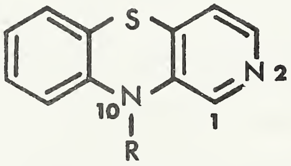
The reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) with CLXXI gave intractable tar and therefore the reaction of 1,2-dihydropyridines with this dienophile was not investigated further.

3.7.0.0.0 Structure-Activity relationships in phenothiazines and azaphenothiazines

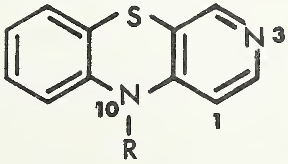
Pyridobenzothiazines (azaphenothiazines) are analogs of phenothiazine in which an annular nitrogen atom forms part of the ring structure. There are four isomeric mono-azaphenothiazines known, namely:



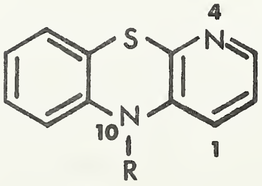
CLXXII



CLXXIII

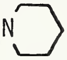
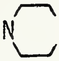


CLXXIV



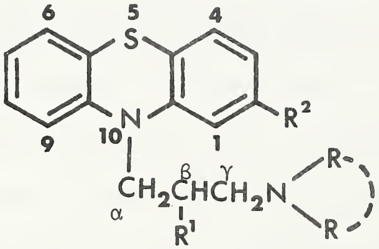
CLXXV

10H-Pyrido[3,2-b][1,4]benzothiazines(1-azaphenothiazines, CLXXII), 10H-pyrido[4,3-b][1,4]benzothiazines(2-azaphenothiazines, CLXXIII), 10H-pyrido[3,4-b][1,4]benzothiazines(3-azaphenothiazines, CLXXIV), and 10H-pyrido[2,3-b][1,4]benzothiazines(4-azaphenothiazines, CLXXV).

The chemistry and pharmacological properties of mono-aza and di-azaphenothiazines have been the subject of a recent review[235]. The pharmacological properties of the 1-azaphenothiazines CLXXII have been examined most thoroughly and a number of derivatives are presently used clinically such as prothipendyl [CLXXII, R = $(CH_2)_3N(Me)_2$], isothipendyl [CLXXII, R = $CH_2CH(Me)N(Me)_2$], pipazethate [CLXXII, R = $CO_2(CH_2)_2O(CH_2)_2$-N], and pervetral [CLXXII, R = $(CH_2)_3$-NN-$(CH_2)_2OH$]. Some of the pharmacological properties exhibited by these agents include sedative, antiemetic, antihistaminic and antitussive activity[235]. In addition to these compounds numerous other derivatives of 1-azaphenothiazines CLXXII, with various R substituents, have been reported with mydriatic[271], tumor inhibiting[272], hypotensive[273], and adrenergic[274] properties. The 1-azaphenothiazines CLXXII (R = $CONH_2$ and CONH-*n*-Pr) which exhibit anticonvulsant activity are of considerable interest[275]. In contrast to the 1-azaphenothiazines CLXXII, 2-aza-CLXXIII, 3-aza-CLXXIV and 4-azaphenothiazine CLXXV derivatives do not exhibit the same degree or spectrum of pharmacological properties.

Versatile preparative reactions for the synthesis of *N*-substituted-1,2-dihydropyridines have been developed[189,190,243]. It was therefore of interest to use these methods to elaborate the pyridyl ring of azaphenothiazines. 1-Azaphenothiazine was selected for investigation from the four known isomeric mono-azaphenothiazines CLXXII-CLXXV since derivatives of the 1-aza-isomer CLXXII had shown the greatest pharmacological potential and were therefore logical choices for study.

It was of interest to determine whether structure-activity relationships in the azaphenothiazine series paralleled those observed with phenothiazine derivatives CLXXVI[300,301] having similar N-10-substituents, viz.



CLXXVI

1) A three carbon side chain connecting N-10 and the more basic side chain nitrogen is optimum for tranquilizing activity. Compounds with a two carbon side chain still possess moderate CNS depressant activity but their antihistaminic and antiparkinsonism effects predominate. If the side chain is altered significantly in length or polarity, tranquilizing activity is lost, although compounds of this type show antitussive properties.

2) Branching at the β-position of the side chain (R^1) with a small group such as methyl reduces tranquilizing potency but may enhance antihistaminic and antipruritic effects. This has been attributed to steric repulsion between the methyl group at the β-position and the 1,9-peri hydrogen on the phenothiazine ring resulting in a decreased coplanarity of the benzene rings. Side chain substitution with a large or polar group such as phenyl, dimethylamino, or hydroxyl results in loss of tranquilizing activity.

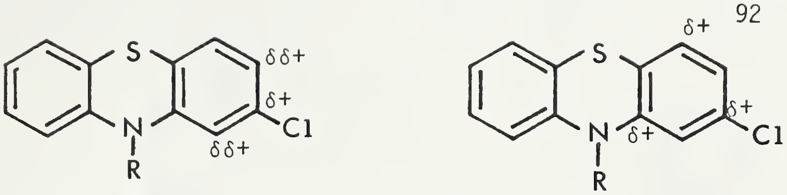
3) Substitution of the terminal dimethylamino group by a piperazine ring enhances potency.

4) Quaternization of the side chain nitrogen results in a decrease in lipid solubility leading to decreased penetration of the CNS and virtual loss of central effects.

Although a particular N-10 substituent is expected to have generally the same effect on the activity of both phenothiazines CLXXVI and 1-azaphenothiazines CLXXII, a similar analogy with respect to ring substitution is not clear. In the phenothiazine series CLXXVI replacement of hydrogen at the C-2 position by a substituent R^2 capable of exerting a negative inductive (-I) effect such as chloro, trifluoromethyl, dimethylsulfonamido, thioalkyl, methoxyl or acetyl enhances activity. On the other hand ring substitution at C-1, C-3, C-4 or simultaneous substitution in both aromatic rings results in loss of tranquilizing activity. It is evident however from the extensive pharmacological properties of 1-azaphenothiazines CLXXII that replacement of the C-1 carbon in CLXXVI with nitrogen does not result in complete loss of activity.

On the basis of this observation we considered the possibility that the ring nitrogen of the 1-azaphenothiazines CLXXII was capable of inducing the same electronic effects as a -I substituent such as chloro, at the C-2 position of the phenothiazine CLXXVII.

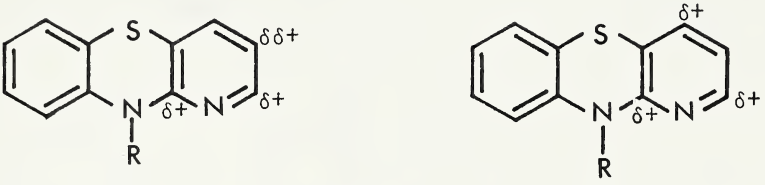
The inductive effect of the 2-chloro substituent in CLXXVII is expected to be strongest at the carbon atom to which it is bonded and to fall off rapidly with distance from this center. The inductive effect of the pyridyl nitrogen in CLXXII is expected to be most



a

b

CLXXVII



a

b

CLXXII

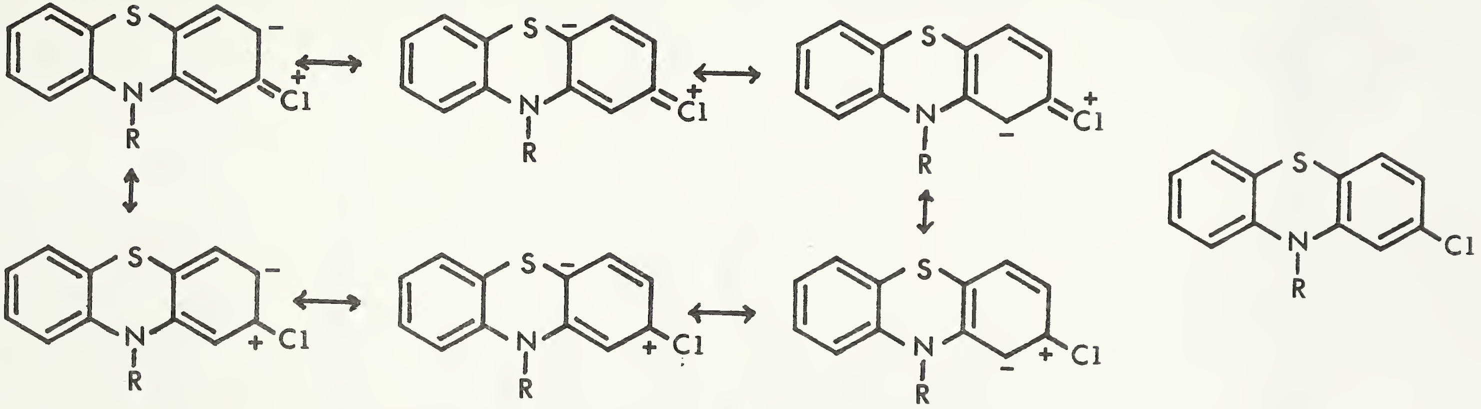
pronounced at the ortho-positions and to decrease as the distance from the nitrogen increases. The overall inductive effect of the C-2 chloro substituent in the phenothiazines and the pyridyl nitrogen in the 1-azaphenothiazines may be illustrated as CLXXVIIa and CLXXIIa respectively.

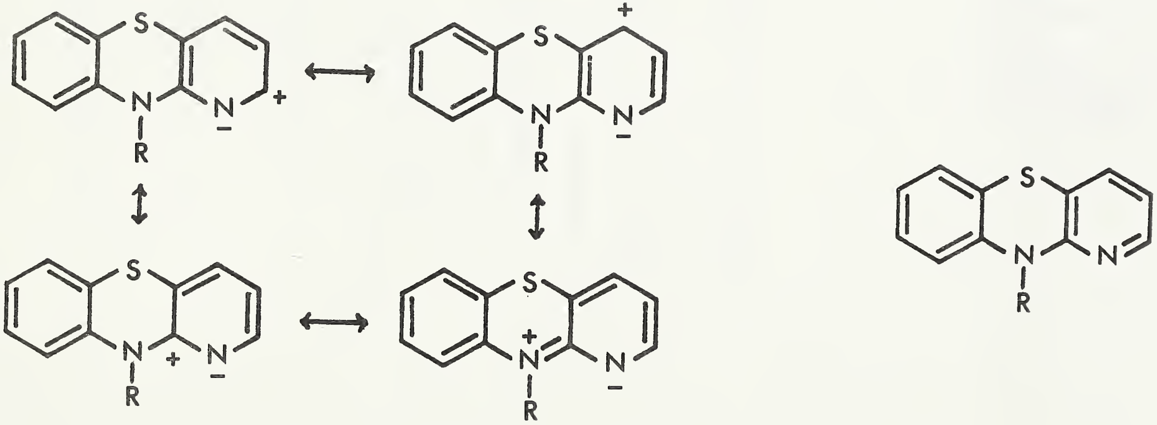
Although other typical C-2 phenothiazine substituents such as trifluoromethyl are not capable of resonance interaction with the ring the positive resonance (+R) effect of the chloro group must also be considered. The phenothiazine CLXXVII and 1-azaphenothiazine CLXXII resonance structures are shown in Figure 1 and may be generalized as CLXXVIIb and CLXXIIb respectively. It is evident from structures CLXXVIIb and CLXXIIb that the same ring positions are electron deficient, namely C-2, C-4, and C-6. Structures CLXXVIIa and CLXXIIa indicate that in both the phenothiazine and 1-azaphenothiazine series the C-2 position is most electron deficient.

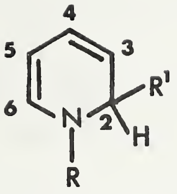
The π-electron density of 1,2-dihydropyridines IC is greatest at the C-3 and C-5 positions[179,181,232]. The chemical shifts of

Figure I

Resonance Structures of Phenothiazines CLXXVII and 1-Azaphenothiazines CLXXII



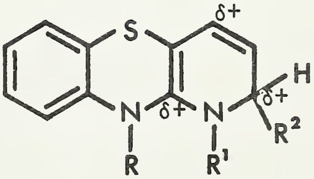




IC

	R	R^1
a	Li	*n*-Bu
b	D	*n*-Bu
c	H	H
c	Li	Ph

1,2-disubstituted-1,2-dihydropyridines[189,190] appear in the following sequence of increasing δ values, $H_6 > H_4 > H_3 > H_5$. The position of H_2 is variable and may appear at higher field than H_5 when R^1 = *n*-Bu, H or between H_6 and H_4 when R^1 = Ph. These observations indicate that the C-6, C-4 (and C-2 when R^1 = Ph) positions have the lowest π electron density. Further precedent in support of a high electron density at C-3 and C-5 of 1,2-dihydropyridines is evident since Friedel-Crafts alkylation and acylation occurs at the C-5 position[276,277]. If these observations may be extrapolated to include a fused 1,2-dihydropyridyl ring the positions of lowest π-electron density may be illustrated as in CLXXVIIIa indicating a close similarity to that observed in CLXXVIIa, b and CLXXIIa, b. Similar electronic effects for the 2-aza, 3-aza, and 4-azaphenothiazines may be summarized as

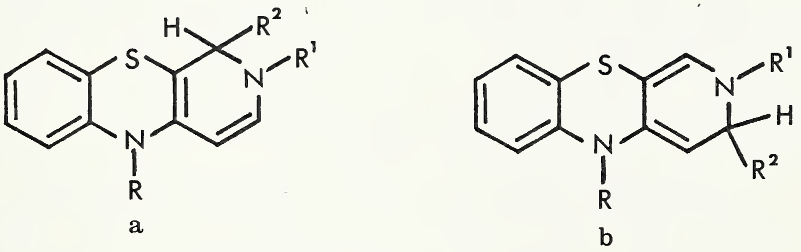


R^2 = Ph

CLXXVIIIa

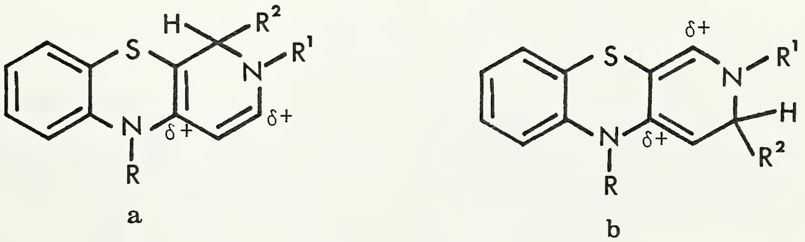
shown in Figure II by CLXXIIIa and b, CLXXIVa and b, and CLXXVa and b. It is immediately obvious that the 3-aza and 1-azaphenothiazines CLXXIVa, b and CLXXIIa, b respectively duplicate most closely the electronic effects observed with the 2-chlorophenothiazines CLXXVIIa and b.

The reaction of 3-azaphenothiazines CLXXIV with organolithium reagents and an electrophile may give rise to two isomeric 1,2-dihydropyridines CLXXIXa and b since the addition may occur in either or both directions. The positions of lowest electron density may be



CLXXIX

illustrated as in CLXXXa and b. It is evident that the electronic distribution in CLXXXa corresponds very well with that observed for CLXXVIIa and b and is superior to that of CLXXVIIIa since the C-2

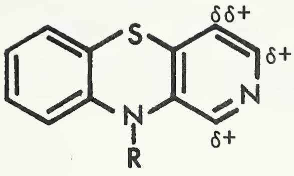


CLXXX

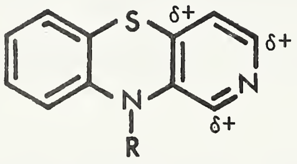
Figure II

Summary of Resonance and Inductive Effects in Phenothiazines and Azaphenothiazines

Inductive Effects   Resonance Effects

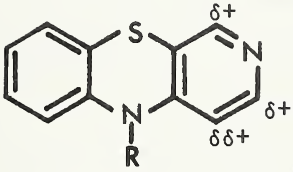


a

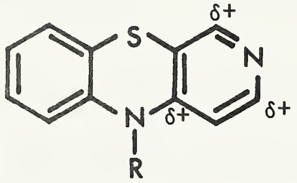


b

CLXXIII

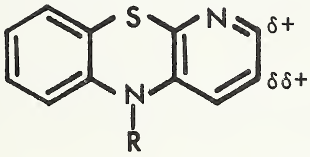


a



b

CLXXIV



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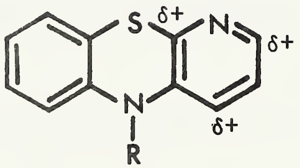
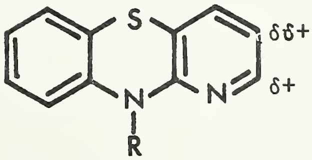
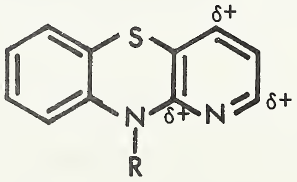


b

CLXXV

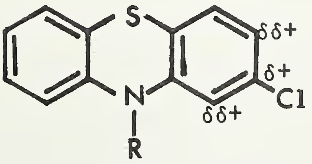


a

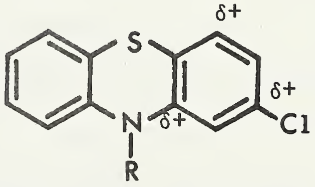


b

CLXXII



a



b

CLXXVII

position of CLXXXa is the most positive center regardless of the nature of the R^2 substituent. This suggests that the 1,2-dihydropyridines derived from the 3-azaphenothiazine series CLXXIV will most closely mimic the pharmacological properties of the 2-chlorophenothiazines CLXXVII. However, a number of other factors determined the final selection of the 1-azaphenothiazine series CLXXII for further elaboration; viz.

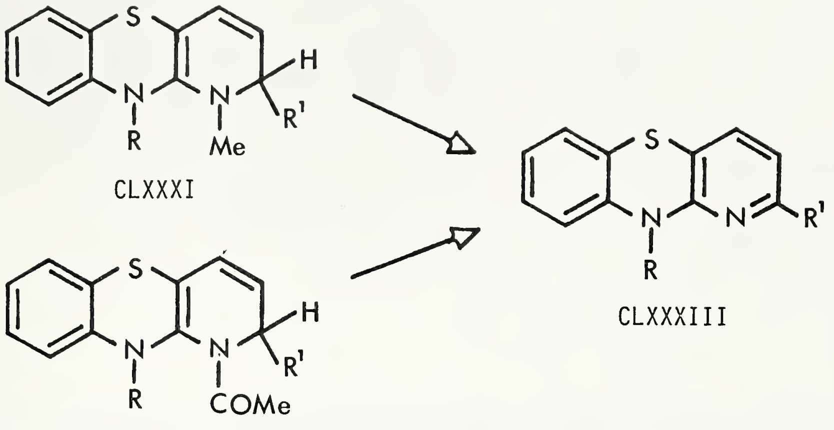
1. The commercial availability of 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXII, R = H) from which 10-substituted-1-azaphenothiazines could be prepared.

2. The possible obtention of two isomers CLXXIXa and b from the 3-azaphenothiazines would profoundly complicate the purification and yield of the reaction products. On the other hand 1-azaphenothiazines CLXXII can give rise to only one 1,2-dihydropyridine derivative CLXXVIII.

3. The pharmacological properties of 1-azaphenothiazines CLXXII were more extensively documented than the 3-aza-isomer CLXXIV.

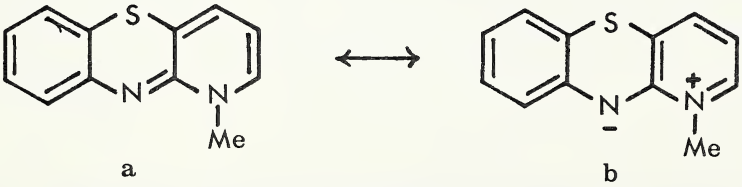
4. If the 1,2-dihydropyridine derivative CLXXVIII does not itself have pharmacological activity it may act as a pro-drug.

The potential biological conversion of compounds CLXXXI and CLXXXII respectively would afford the more stable aromatic compounds CLXXXIII which are known to be pharmacologically active. Precedence for this postulate is borne out by the observation that N-methyl-1,6-dihydropyridine-2-carbaldoxime (XIV) is an efficient pro-drug of N-methylpyridinium-2-carbaldoxime chloride (XV)[35]. Results in this laboratory suggest[278] that some N-acetyl-1,2-dihydropyridines may undergo



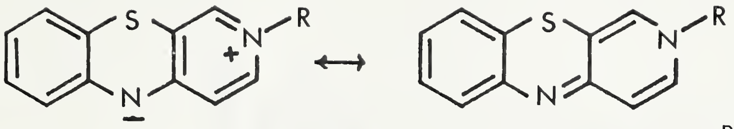
aromatization to give the corresponding aromatic compound CLXXXIII as shown above.

To our knowledge there is only one report describing the existence of a 1-azaphenothiazine having a 1,2-dihydropyridyl ring as part of the fused ring system. Schuler and Klebe reported^{244} the preparation of 1-aza-1-methyl-1,2-dihydrophenothiazine CLXXXIV for which no pharmacological data is available. It is likely that



CLXXXIV

CLXXXIVa is in resonance with the anhydronium base CLXXXIVb in view of the report that $\underline{N}^{3}$-substituted-3-azaphenothiazines CLXXXVa are in resonance with the anhydronium bases CLXXXVb^{279}.



a b

CLXXXVa

R = $(CH_2)_3N(Me)_2$
$(CH_2)_3NC_5H_{10}$
$(CH_2)_2NH_2$
Me

3.8.0.0.0 Reaction of 10-alkyl-10H-pyrido[3,2-b][1,4]benzothiazines with *n*-butyllithium and electrophilic reagents

See Scheme VII and Table IX.

3.8.1.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with *n*-butyllithium and electrophilic reagents

10-Methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) was prepared from reaction of 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) with sodium hydride and iodomethane.

Sodium hydride was found to be the most effective base for abstraction of the N-10 proton from 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa).

3.8.1.1.0 Reaction with *n*-butyllithium and methyl chloroformate

Reaction of CLXXIIb with *n*-butyllithium and methyl chloroformate gave CLXXVIIIa and CLXXXVIIa in 79.7% and 19.8% yield respectively (see Table IX). The structures of CLXXVIIIa and CLXXXVIIa were assigned on the basis of their spectral properties.

Scheme VII

Reaction of 1-Azaphenothiazines with n-Butyllithium and Electrophilic Reagents

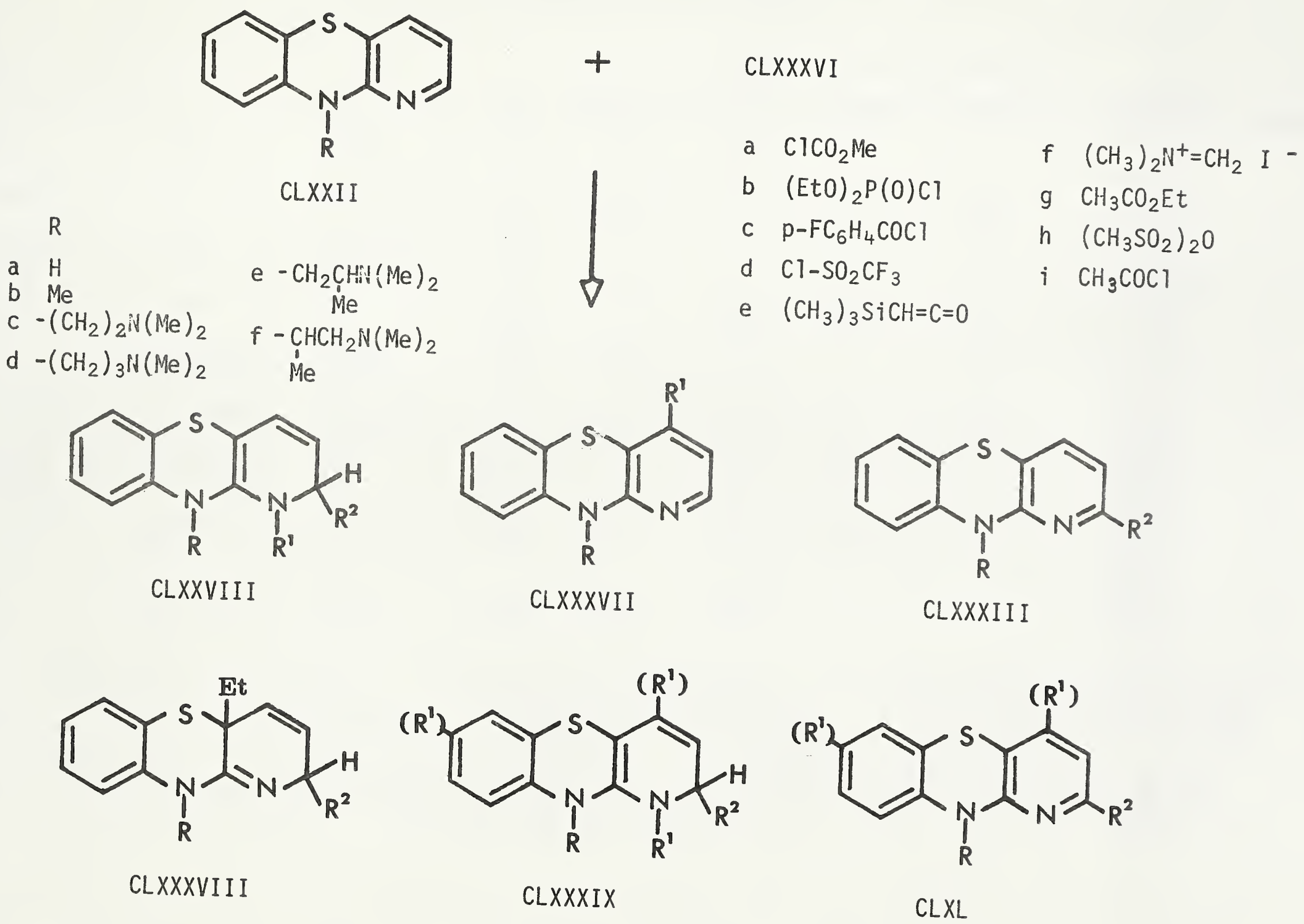


TABLE IX

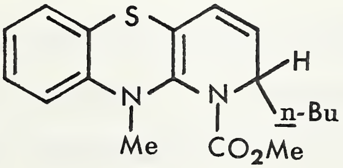
Percent Yield of Products from Reaction of Electrophilic Reagents with *n*-Butyllithium-10H-Pyrido[3,2-b][1,4]benzothiazine adducts

				Percent Yield of Products						
CLXXXVI	R	R^1	R^2	CLXXVIII	CLXXXVII	CLXXXIII	CLXXXVIII	CLXXXIX	CLXL	Comments
(a) $ClCO_2Me$	Me	$-CO_2Me$	*n*-Bu	79.7	19.8	-	-	-	-	-
(b) $(EtO)_2P(O)Cl$	Me	$(EtO)_2P(O)-$	*n*-Bu	24.8	17.9	3	8.3	-	-	1
(c) $p-FC_6H_4COCl$	Me	$p-FC_6H_4CO-$	*n*-Bu	-	-	-	-	35	2.5	2,3
(d) $Cl-SO_2CF_3$	Me	$-Cl$	*n*-Bu	-	14.5	44.4	-	-	-	4
(e) $ClCO_2Me$	$-(CH_2)_3N(Me)_2$	$-CO_2Me$	*n*-Bu	31.4	7.5	-	-	-	-	5,6
(f) $(EtO)_2P(O)Cl$	$-(CH_2)_3N(Me)_2$	$(EtO)_2P(O)-$	*n*-Bu	16.7	9.3	-	2.5	-	-	7
(g) $Cl-SO_2CF_3$	$-(CH_2)_3N(Me)_2$	$-Cl$	*n*-Bu	-	8.3	27.7	-	-	-	8
(h) $(EtO)_2P(O)Cl$	$-CH_2\underset{Me}{C}HN(Me)_2$	$(EtO)_2P(O)-$	*n*-Bu	14.1	7.9	2.4	-	-	-	9
(i) $ClCO_2Me$	$-CH_2\underset{Me}{C}HN(Me)_2$	$-CO_2Me$	*n*-Bu	38.5	8.5	-	-	-	-	10

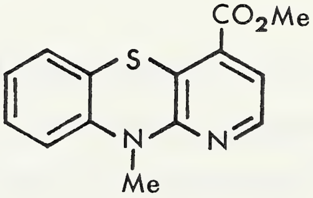
Comments: 1. Recovered 6.6% CLXXIIb. 2. Recovered 10.2% CLXXIIb. 3. The R^1 substituent of CLXL and CLXXXIX is at the C-4 or C-7 position. 4. Recovered 5.2% CLXXIIb. 5. Purification by column chromatography on silica gel gave CLXXVIII in 54.5% yield. 6. Recovered 12.3% CLXXIId. 7. Recovered 12.9% CLXXIId. 8. Recovered 3.1% CLXXIId. 9. CLXXXVIIIh was also detected in the nmr spectrum of the thin layer fraction (R_f 0.69) but it could not be isolated in sufficient amount to allow unequivocal characterization. 10. Recovered 12% CLXXIIe.

The nmr spectrum (δ) of CLXXVIIIa exhibited a four H multiplet at 6.66 - 7.26 attributed to the phenyl hydrogens. The C_3-H and C_4-H signals appeared as a two H multiplet from 5.48 - 5.92 and the broad one H multiplet at 4.8 was assigned to the C_2-H. The O-methyl and N-methyl absorptions appeared as three H singlets at 3.7 and 3.18 respectively while the n-butyl absorption consisted of a broad nine H multiplet from 0.68 - 1.98. The ir spectrum (cm^{-1}) exhibited absorptions at 1725 (C=O) and 1632 and 1568 (C=C) while the mass spectrum displayed a molecular ion corresponding to $C_{18}H_{22}N_2O_2{}^{32}S$: Mass calculated, 330.1397; found, 330.1400. These assignments are consistent with the structure N-methoxycarbonyl-2-n-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIa).

The nmr spectrum (δ) of CLXXXVIIa exhibited a one H doublet ($J_{2,3}$ = 5) at 8.03 assigned to the C_2-H while the C_3-H appeared as a doublet ($J_{2,3}$ = 5) at 7.19. The four H multiplet from 6.6 - 7.36 was attributed to the phenyl hydrogens while the O-methyl and N-methyl absorptions appeared as three H singlets at 3.94 and 3.39 respectively. The ir spectrum (cm^{-1}) exhibited an absorption at 1711 (C=O) while the mass spectrum displayed a molecular ion corresponding to $C_{14}H_{12}N_2O_2{}^{32}S$: Mass calculated, 272.0617; found, 272.0615. These assignments are consistent with the structure 4-methoxycarbonyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXVIIa).



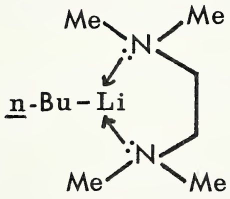
CLXXVIIIa



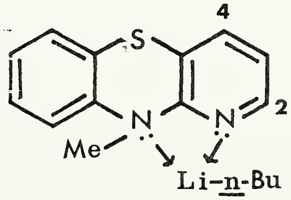
CLXXXVIIa

The formation of CLXXXVIIa provides the first example of proton abstraction from the 4-position of a pyridine ring in any of our studies involving pyridines and organolithium reagents to date.

Organolithium compounds are considered electron deficient, a property characterized by the formation of polymeric species through delocalization of one or more bonding electron pairs. These polymers, in turn, exhibit Lewis acid character since they form addition compounds with n-type bases such as amines or ethers[280]. n-Butyllithium is believed to be a hexameric species in hydrocarbon solvents and a tetrameric species in ethereal solvents due to coordination with the solvent. The addition of a more powerful Lewis base, such as N,N,N',N'-tetramethylethylenediamine, converts n-butyllithium entirely into a coordinated monomeric reagent[281]. The resulting complex CLXLI is an extremely powerful base capable of effecting deprotonation in examples where n-butyllithium itself is inert. A similar complex CLXLII might be formed from the reaction of CLXXIIb and n-butyllithium. Since n-butyllithium itself is not expected to be a sufficiently strong base to effect deprotonation of a C-4 pyridyl proton it is postulated that

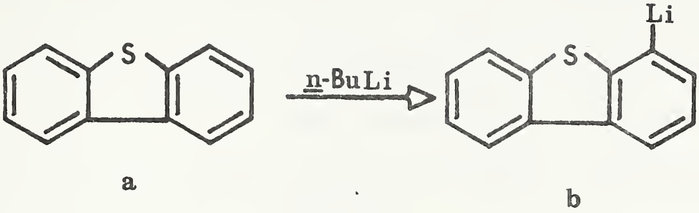


CLXLI



CLXLII

the complex CLXLII is involved in the formation of CLXXXVIIa. The abstraction of a C-4 proton rather than C-2 may be explained in view of the known ortho-directing influence of a sulfur atom. Dibenzothiophene (CLXLIIIa) is easily metalated by n-butyllithium to give



CLXLIII

CLXLIIIb[282] particularly if tetrahydrofuran is used as the solvent[283]. It is not unreasonable to suggest that the sulfur in CLXXIIb similarly directs metalation to the C-4 position of the pyridyl ring. Reaction with methyl chloroformate would then afford CLXXXVIIa.

3.8.1.2.0 Reaction with n-butyllithium and diethyl chlorophosphate

Reaction of CLXXIIb with n-butyllithium and diethyl chlorophosphate gave CLXXVIIIb, CLXXXVIIb, CLXXXIIIb, CLXXXVIIIb, and CLXXIIb in 24.8%, 17.9%, 3%, 8.3% and 6.6% yield respectively (see Table IX). The structures of these compounds were assigned on the basis of their spectral properties.

The nmr spectrum (δ) of CLXXVIIIb exhibited a four H multiplet at 6.68 - 7.35 attributed to the phenyl hydrogens. The C_3-H and C_4-H absorptions appeared as a two H multiplet at 5.32 - 5.91 while the broad five H multiplet at 3.59 - 4.52 was due to the C_2-H and the two

methylenes of the ethoxyl groups. The N-methyl signal was a three H singlet at 3.36 and the fifteen H multiplet at 0.58 - 1.92 was attributed to the n-butyl substituent and the two methyls of the ethoxyl groups. The ir spectrum (cm^{-1})exhibited absorptions at 1273 (P=O) and at 1630 and 1567 (C=C) while the mass spectrum exhibited a molecular ion corresponding to $C_{20}H_{29}N_2O_3P^{32}S$: Mass calculated, 408.1630; found, 408.1635. These assignments are consistent with the structure N-diethylphosphoryl-2-n-butyl-10-methyl-1,2-dihydropyridyl-[3,2-b][1,4]benzothiazine (CLXXVIIIb).

The nmr spectrum (δ) of CLXXXVIIb exhibited a one H triplet ($J = 5$) at 8.14 assigned to the C_2-H. The multiplicity of this signal as shown in Figure IV.was attributed to the coupling of the C_2-H with the C_3-H ($J = 5$) and long range coupling with P^{31} ($J = 5$). The five H multiplet from 6.72 - 7.3 was assigned to the C_3-H and phenyl hydrogens and the four H multiplet centered at 4.25 was due to the two methylenes of the ethoxyl groups. The N-methyl signal appeared as a three H singlet at 3.44 while the two methyls of the ethoxyl group appeared as a six H triplet ($J = 7$) at 1.36. The ir spectrum (cm^{-1}) exhibited an absorption at 1265 (P=O) while the mass spectrum displayed a molecular ion corresponding to $C_{16}H_{19}N_2O_3P^{32}S$: Mass calculated, 350.0850; found, 350.0846. These assignments are consistent with the structure 4-diethylphosphoryl-10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXXVIIb).

The nmr spectrum of CLXXXIIIb was identical to that of a fully characterized sample of 2-n-butyl-10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXXIIIb) obtained from the thermal treatment of the

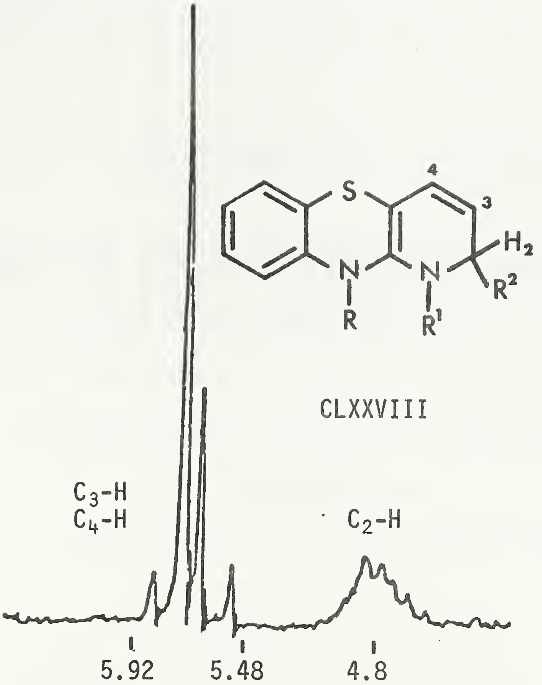


Figure III: Typical Splitting Pattern for the 1,2-dihydropyridyl hydrogens of 10-substituted-1,2-dihydropyridyl[3,2-b]-[1,4]benzothiazines, CLXXVIII.

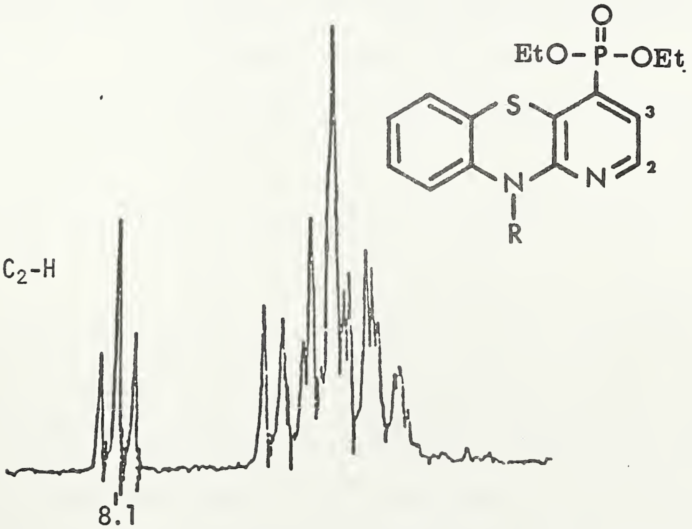
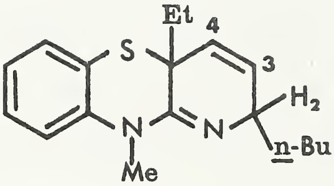


Figure IV: Typical Splitting Pattern for the C_2-H of 4-Diethylphosphoryl-10-substituted-10H-pyrido[3,2-b][1,4]-benzothiazines.

10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb)-n-butyllithium adduct.

The nmr spectrum (δ) of CLXXXVIIIb exhibited a four H multiplet from 6.68 - 7.44 attributed to the phenyl hydrogens. The one H doublet ($J_{3,4}$ = 10) of doublets (J = 1.75) at 6.12 and the one H doublet ($J_{3,4}$ = 10) of doublets (J = 2) at 5.64 was assigned to either the C_3-H or C_4-H. $J_{3,4}$ is expected to be 7 - 10 Hz (J_{cis}) while $J_{2,4}$ should be in the order of 0 - 3 Hz (allylic coupling).

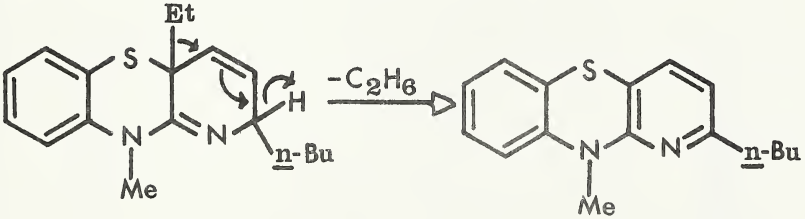


CLXXXVIIIb

$J_{2,3}$ is expected to be 4 - 10 Hz (allylic coupling) but Drieding models suggest a C_2-H - C_3-H dihedral angle corresponding to J ≅ 1-2 Hz from the Karplus curve. On the basis of the nmr data it could not be determined which multiplet (6.12 or 5.64) was due to which hydrogen (C_3-H or C_4-H). The broad one H multiplet at 4.18 was assigned to the C_2-H while the three H singlet at 3.58 was due to the N-methyl substituent. The eleven H multiplet from 0.59 - 2 was due to the n-butyl group and the methylene of the ethyl substituent while the triplet (J = 7) at 0.7 was assigned to the methyl of the ethyl group. These assignments were confirmed by double resonance studies (FiguresV-1,2). Irradiation (δ) at 4.18 (C_2-H) simplified the C_3-H and C_4-H signals

to a doublet ($J_{3,4}$ = 10) respectively due to loss of $J_{2,4}$ and $J_{2,3}$. Irradiation at 6.12 and 5.64 (C_3-H and C_4-H) simplified the C_2-H absorption at 4.18 due to loss of $J_{2,3}$ and $J_{2,4}$.

Addition of deuterium oxide to the nmr sample did not change the spectrum. The ir spectrum (cm^{-1}) exhibited a strong absorption at 1631 and a weak band at 1677 (C=C, C=N) while the mass spectrum displayed a molecular ion corresponding to $C_{18}H_{24}N_2{}^{32}S$: Mass calculated, 300.1655; found, 300.1651. These assignments are consistent with the structure 2-n-butyl-4a-ethyl-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]-benzothiazine (CLXXXVIIIb). After the nmr spectrum of CLXXXVIIIb had been determined the sample was left in the nmr tube for one week and the spectrum was determined once again. The appearance of a triplet at 2.75 indicated that the conversion CLXXXVIIIb to CLXXXIIIb was taking place.



CLXXXVIIIb CLXXXIIIb

3.8.1.3.0 Reaction with n-butyllithium and p-fluorobenzoyl chloride

Reaction of CLXXIIb with n-butyllithium and p-fluorobenzoyl chloride gave CLXXXIXc (35%), CLXLc (2.5%) and CLXXIIb (10.2%) as shown in Table IX.

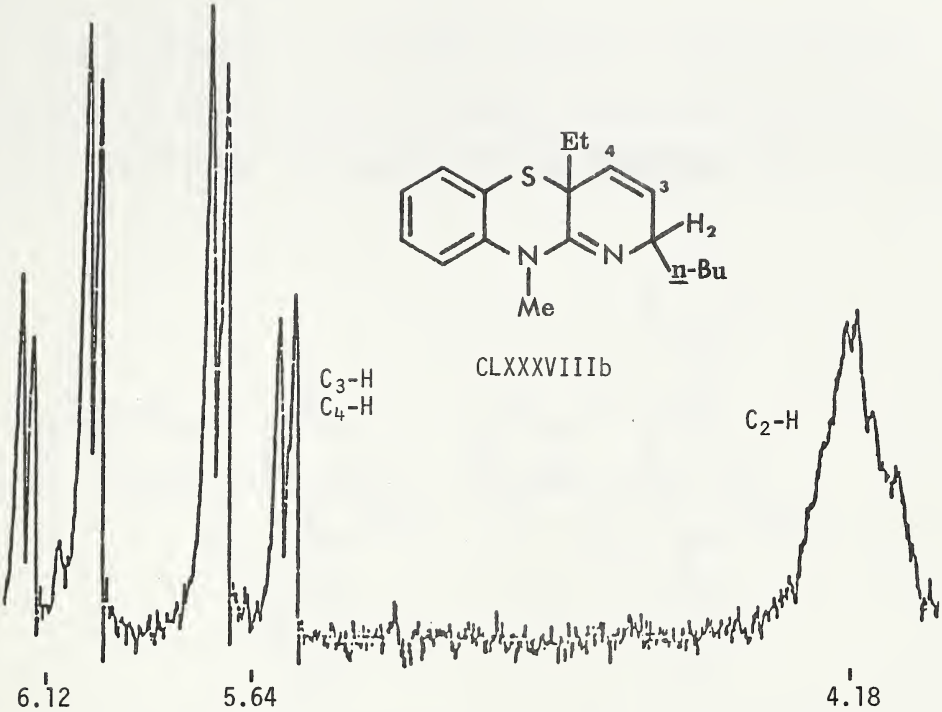


Figure V-1: Splitting Pattern for the 2,4a-Dihydropyridyl hydrogens of 2-n-Butyl-4a-ethyl-10-methyl-2,4a-dihydropyridyl-[3,2-b][1,4]benzothiazine (CLXXXVIIIb).

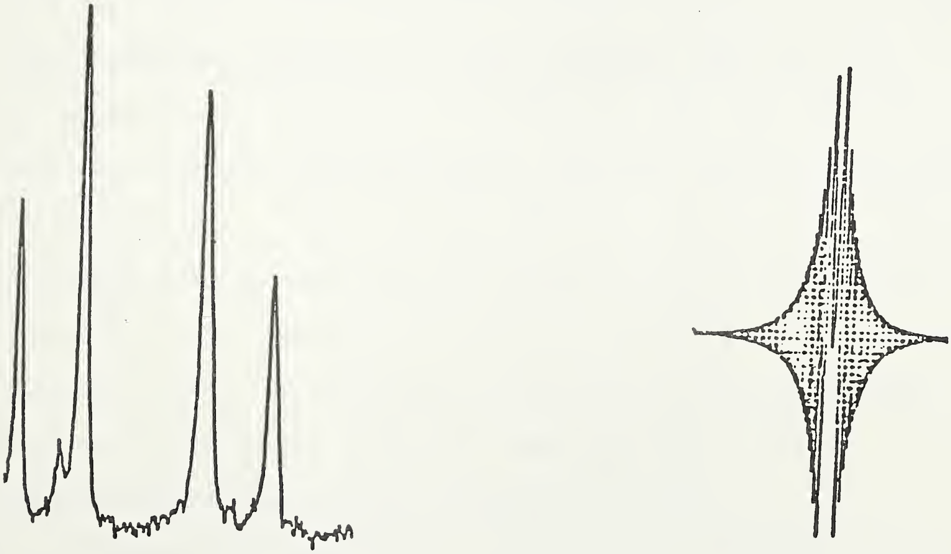
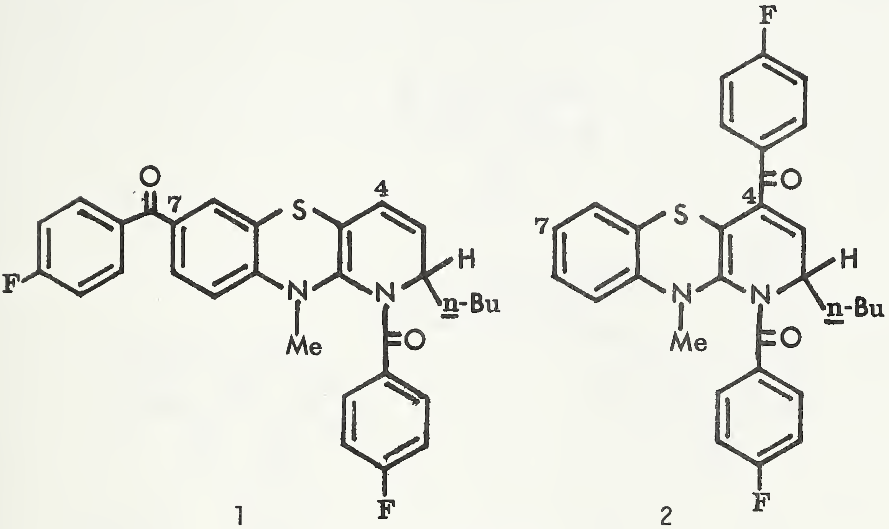


Figure V-2: Irradiation of the C$_2$-H of CLXXXVIIIb.

The nmr spectrum (δ) of CLXXXIXc exhibited a twelve H multiplet from 6.64 - 7.82 attributed to the phenyl hydrogens and the C_4-H (or C_7-H). The C_2-H and C_3-H appeared as a two H multiplet from 5.6 - 6.11



1 2

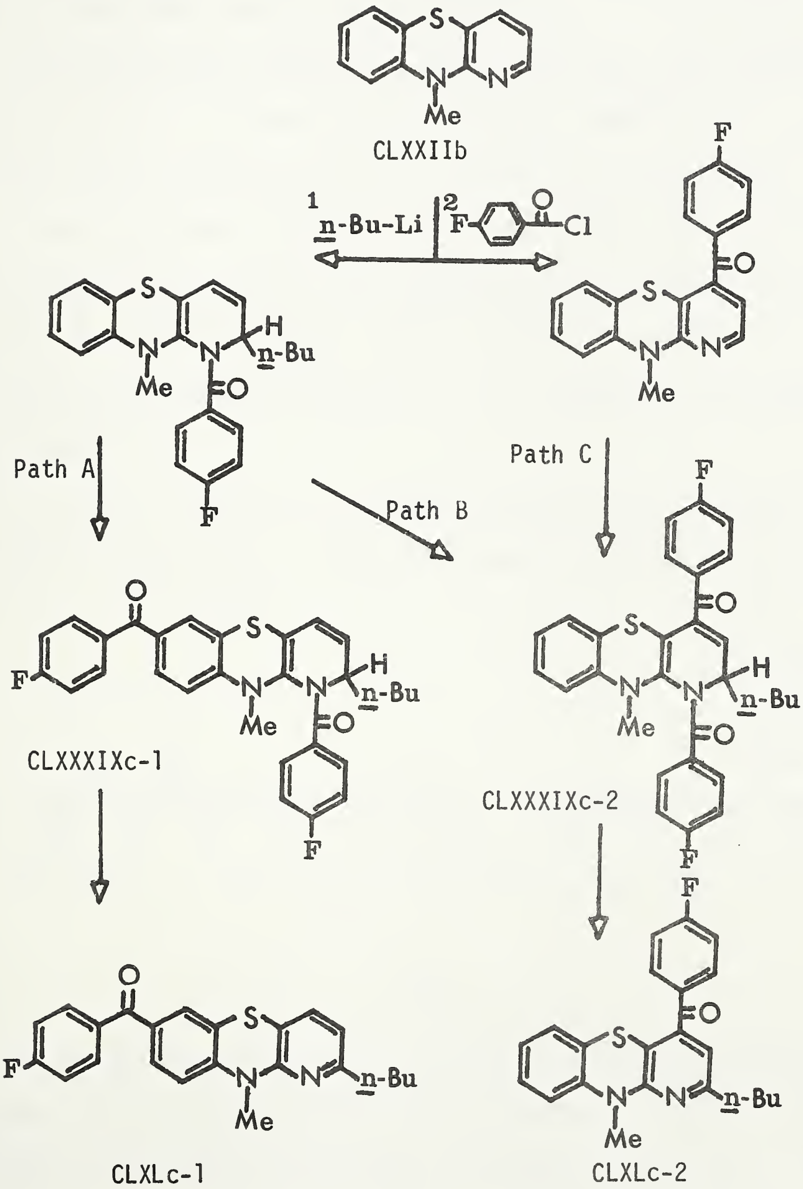
CLXXXIXc

while the N-methyl signal appeared as a three H singlet at 3.08. The n-butyl absorption appeared as a nine H multiplet from 2.08 - 0.77. The ir spectrum (cm^{-1}) exhibited absorptions at 1681 (C=O) and 1635 (C=C) while the mass spectrum displayed a molecular ion corresponding to $C_{30}H_{26}N_2O_2{}^{32}SF_2$: Mass calculated, 516.1677; found, 516.1680. These assignments are consistent with the structure 1,4-(or 7-)di-p-fluorobenzoyl-2-n-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXXIXc-1 or 2). It could not be determined from the nmr spectral evidence whether the p-fluorobenzoyl substituent was at the C-4 position CLXXXIXc-2 or at the C-7 position CLXXXIXc-1.

Some plausible mechanisms for the formation of CLXXXIXc are illustrated in Scheme VIII. The reaction of CLXXIIb with n-butyllithium

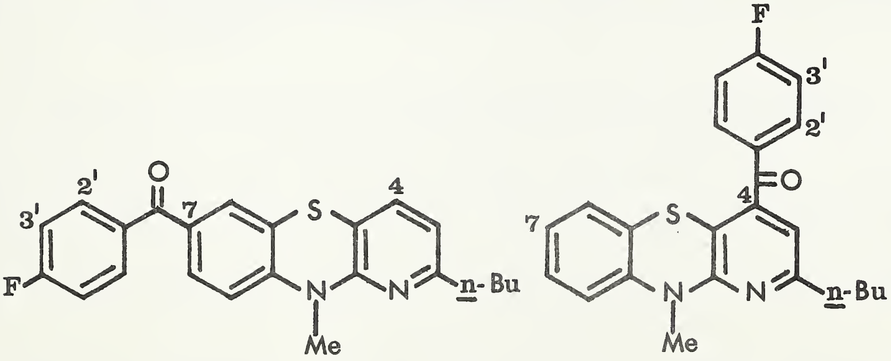
Scheme VIII

Possible Pathways for the Formation of Products from the Reaction of 10-Methyl-10H-pyrido[3,2-b][1,4]benzothiazine-n-Butyllithium Adduct with p-Fluorobenzoyl Chloride



and p-fluorobenzoyl chloride should afford the expected N-substituted-1,2-dihydropyridine and 4-substituted-1-azaphenothiazine compounds. The 1,2-dihydropyridine could then react further by two paths; viz: Path A which involves electrophilic substitution at the C-7 position, and Path B which would require metalation at C-4 followed by acylation. The 4-substituted-1-azaphenothiazine could also react further via Path C to give the 1,4-disubstituted compound. Mechanistically, Paths B and C are unlikely and on this basis CLXXXIXc is probably the 1,7-disubstituted compound CLXXXICc-1. However, the nmr spectrum of CLXXXICc-1 in the 4 - 6 δ region is not expected to be distinctly different from that shown in Figure III. The nmr spectrum of CLXXXIXc in fact exhibits only a two H multiplet from 5.6 - 6.11 δ suggesting that the structure is CLXXXIXc-2.

The nmr spectrum (δ) of CLXLc exhibited a two H doublet ($J_{2',3'}$ = 10) of doublets ($J_{2',F}$ = 6) at 7.8 assigned to the $C_{2'}$ hydrogens. The seven H multiplet from 6.73 - 7.39 was attributed to the remaining phenyl and pyridyl hydrogens while the three H singlet at 3.5 was due to the N-methyl substituent. The two H triplet (J = 7) at 2.72



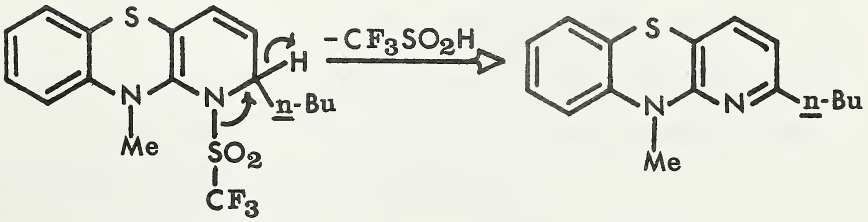
1 2

CLXLc

is due to the α-methylene of the n-butyl group while the remaining n-butyl hydrogens appear as a seven H multiplet at 0.72 - 2.01. The ir spectrum exhibited an absorption at 1660 (C=O) while the mass spectrum exhibited a molecular ion corresponding to $C_{23}H_{21}N_2O^{32}SF$: Mass calculated, 392.1354; found, 392.1359. These assignments are consistent with the structure 2-n-butyl-4-(or 7-)p-fluorobenzoyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLc-1 or 2). It could not be determined from the nmr spectral evidence whether the p-fluorobenzoyl substituent was at the C-4 position CLXLc-2 or at the C-7 position CLXLc-1. Compounds CLXLc-1 and CLXLc-2 could arise as shown in Scheme VII from CLXXXIXc-1 and CLXXXIXc-2 respectively via loss of the N'-substituent as p-fluorobenzaldehyde. This route is plausible in view of the low yield (2.5%) of CLXLc obtained.

3.8.1.4.0 Reaction with n-butyllithium and trifluoromethanesulfonyl chloride

Reaction of CLXXIIb with n-butyllithium and trifluoromethanesulfonyl chloride gave CLXXXIIId (44.4%), CLXXXVIId (14.5%) and unreacted CLXXIIb (5.2%) as shown in Table IX. The high yield of CLXXXIIId was not expected since the reaction of 1-azaphenothiazines CLXXIIb, d and e



CLXXVIIId

CLXXXIIId

with the electrophiles diethyl chlorophosphate, methyl chloroformate and p-fluorobenzoyl chloride gave very low yields of CLXXXIII. In some reactions CLXXXIII was not detected (see Table IX). On the other hand, reaction of the 1-azaphenothiazines CLXXIIb and d with trifluoromethanesulfonyl chloride gave CLXXXIIId in 44.4% and 27.7% yield respectively. These high yields suggest that CLXXXIIId arises from CLXXVIIId _via_ fission of the N^1-S bond with loss of CF_3SO_2H since this bond is expected to be quite labile due to the strong-I effect of the trifluoromethyl group. The facile elimination of CF_3SO_2H adds further credence to the possibility of utilizing CLXXVIII-type compounds as pro-drugs.

The nmr spectrum (δ) of CLXXXVIId exhibited a one H doublet ($J_{2,3}$ = 5.5) at 7.89 due to the C_2-H. The four H multiplet from 6.8 - 7.33 was attributed to the phenyl hydrogens while the C_3-H signal appeared as a one H doublet ($J_{2,3}$ = 5.5) at 6.76. The N-methyl absorption appeared as a three H singlet at 3.39. The nmr spectrum was consistent with the structure 4-trifluoromethanesulfonyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXVII, $R^1 = SO_2CF_3$). However, the mass spectral data did not confirm this structure. Elemental analysis subsequently indicated that the R^1 functionality was not the trifluoromethanesulfonyl group but rather a chloro substituent. The mass spectrum displayed a molecular ion corresponding to $C_{12}H_9N_2{}^{32}S^{37}Cl$: Mass calculated, 250.0144; found, 250.0141; and $C_{12}H_9N_2{}^{32}S^{35}Cl$: Mass calculated, 248.0174; found, 248.0168. These results are consistent with the structure 4-chloro-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXVIId).

Two possible pathways for the formation of the unexpected 4-chloro-compound CLXXXVIId are shown in Scheme IX. Path A involves nucleophilic attack at chlorine, the driving force being elimination of sulfur dioxide and a trifluoromethyl carbanion which is stabilized by the strong -I effect of the fluorine substituents. Alternatively, Path B involves chlorine-lithium exchange to give CLXXXVIIb.

3.8.2.0.0 Reaction of 10-(3-dimethylaminopropyl), 10-(2-dimethylaminopropyl), and 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine with *n*-butyllithium and electrophilic reagents.

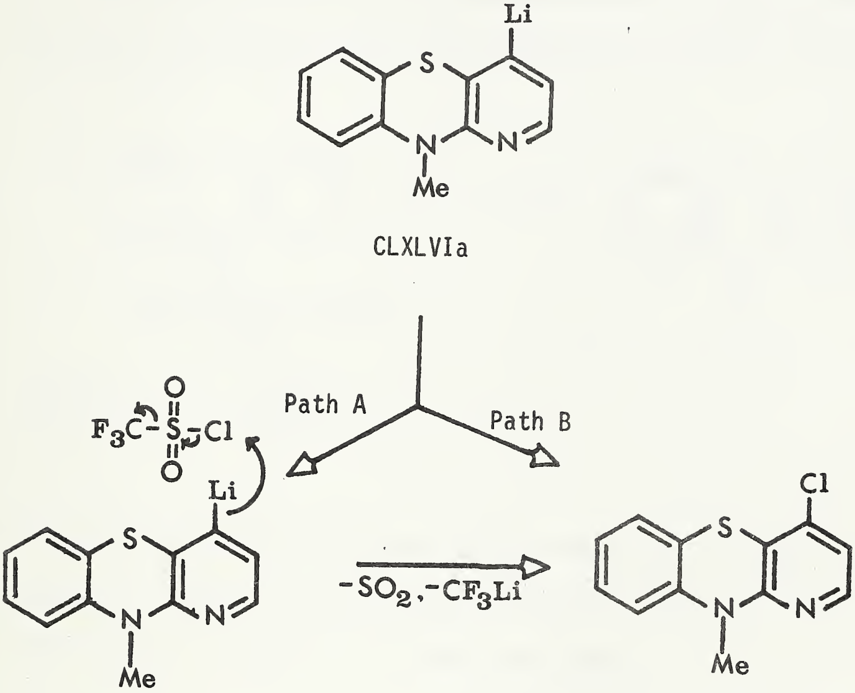
10-(3-Dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) was prepared from its hydrochloride salt (Tolnate) using potassium carbonate.

Alkylation of 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) with sodium hydride and 2-dimethylaminoisopropyl chloride hydrochloride gave the 1-azaphenothiazines CLXXIIe and f which were separated by column chromatography on silica gel. Compound CLXXIIe is the major product confirming the work of Yale and Sowinski who separated the two isomers by fractional crystallization as the monohydrochlorides[305]. These results parallel those observed in the phenothiazine series[306].

The per cent yield of products obtained from the reaction of CLXXIId and e with *n*-butyllithium and electrophilic reagents is shown in Table IX. All products were fully characterized on the basis of their spectral properties.

Scheme IX

Possible Pathways for the Formation of 4-Chloro-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine

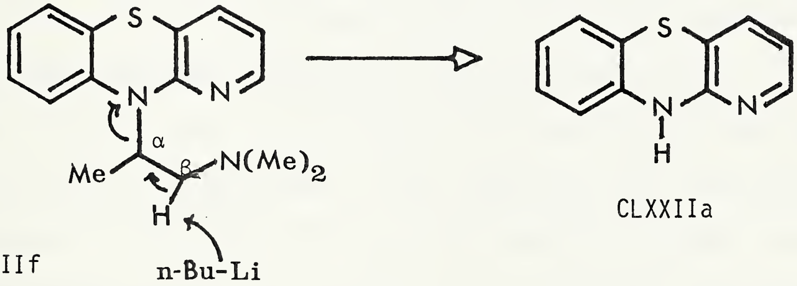


CLXLVIa

CLXXXVIId

3.8.3.0.0 Reaction of 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine with n-butyllithium and methyl chloroformate

Reaction of CLXXIIf with n-butyllithium and methyl chloroformate afforded 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) in 15.2% yield.



CLXXIIf

CLXXIIa

Product CLXXIIa could arise as shown above or as a result of attack by n-butyllithium at the α-carbon of CLXXIIf. The nmr and mp of CLXXIIa were identical to that of an authentic sample.

3.8.4.0.0 Reaction of 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with n-butyllithium and electrophilic reagents

10-(2-Dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIc) was prepared from reaction of 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) with sodium hydride and 2-dimethylaminoethyl chloride hydrochloride.

3.8.4.1.0 Reaction with n-butyllithium and methyl chloroformate

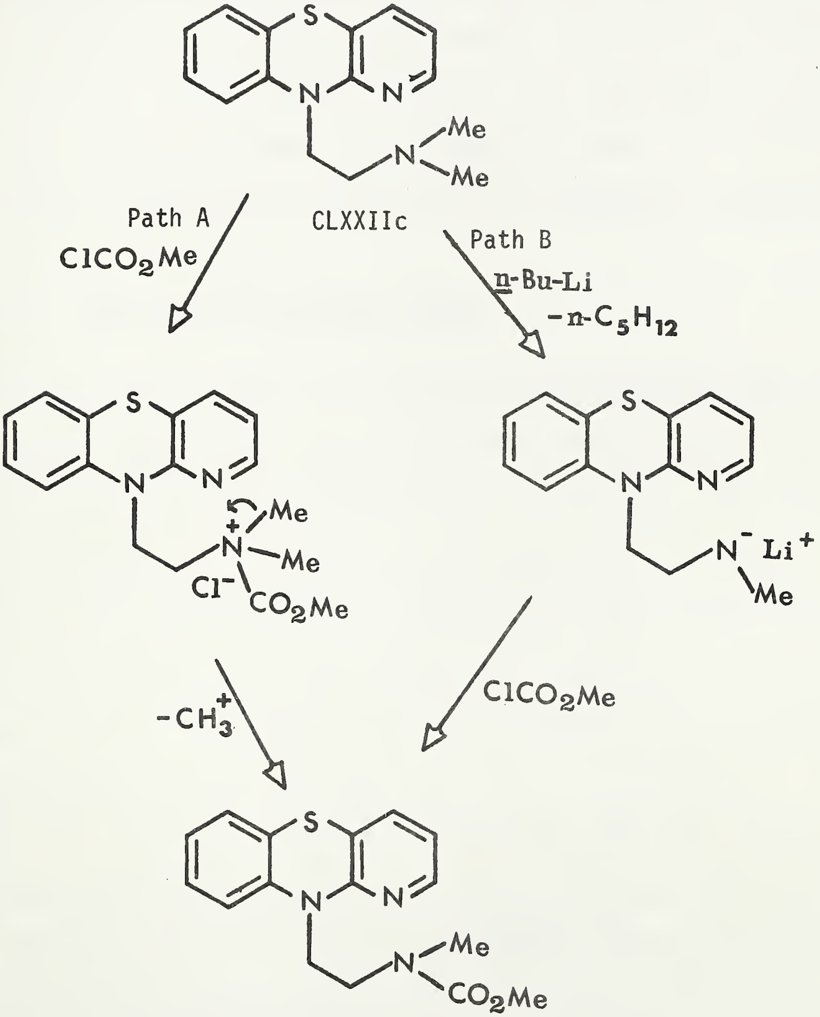
Reaction of CLXXIIc with n-butyllithium and methyl chloroformate afforded CLXLIV (24.4%) and starting material CLXXIIc (32.1%).

The nmr spectrum (δ) of CLXLIV exhibited a one H doublet ($J_{2,3}$ = 5) of doublets ($J_{2,4}$ = 1.75) at 8 assigned to the C_2-H. The six H multiplet at 6.59 - 7.34 was attributed to the C_3-H, C_4-H and phenyl hydrogens. The two H multiplet at 4.29 is due to the α-methylene while the β-methylene appears as a two H multiplet at 3.51 - 3.95. The three H singlets due to the O-methyl and N-methyl substituents appear at 3.74 and 3.04 respectively. The ir spectrum (cm^{-1}) exhibited an absorption at 1710 (C=O) while the mass spectrum displayed a molecular ion corresponding to $C_{16}H_{17}N_3O_2{}^{32}S$: Mass calculated, 315.1038; found, 315.1042. These assignments are consistent with the structure 10-(2-N-methoxycarbonyl-2-N-methylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLIV). Possible pathways for the formation of the unexpected N-demethylated product are shown in Scheme X. Path B involves attack by n-butyllithium at a methyl substituent with loss of pentane. Acylation of the resulting anion with methyl chloroformate would then give CLXLIV. This path is probably unlikely as there is no apparent reason why n-butyllithium would displace the relatively non-electrophilic methyl substituent.

Replacement of an N-methyl group with an N-alkoxy-, aryloxy-, or arylalkoxycarbonyl group has been reported. Thus treatment of codeine[290], tropine[291] and erythromycin[292] with ethyl chloroformate gave the corresponding N-ethoxycarbonyl product resulting from the loss of the N-methyl substituent as chloromethane. This method

Scheme X

Possible Pathways for the Formation of 10-(2-N-Methoxycarbonyl-2-N-methylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine



CLXLIV

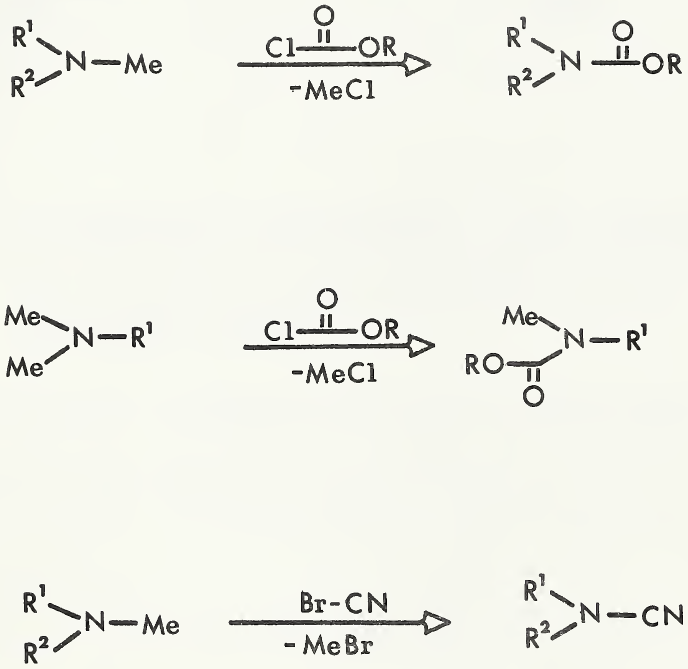
supplements the von Braun reaction[302] which employs cyanogen bromide rather than a chloroformate ester to effect N-demethylation. These procedures are illustrated as general equations shown in Scheme XI. The N-cyano or N-alkoxycarbonyl groups are generally hydrolyzed to give the corresponding N-unsubstituted amine product. A recent report[293] describing the reaction of apomorphine with methyl chloroformate indicates that this carbamate is also capable of effecting N-demethylation. In view of these results it appears that CLXLIV may be formed via Path A as shown in Scheme X. The N-methyl group is probably lost as a methyl carbonium ion in the form of chloromethane or n-pentane.

3.8.4.2.0 Reaction with n-butyllithium

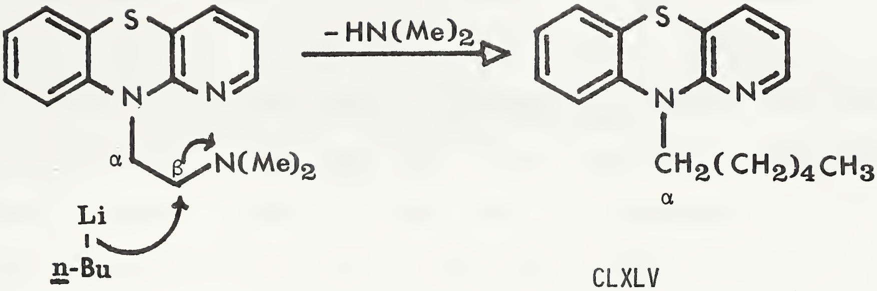
The reaction of CLXXIIc with n-butyllithium afforded CLXLV in 25.9% yield. The nmr spectrum (δ) exhibited a one H doublet ($J_{2,3} = 5$) of doublets ($J_{2,4} = 1.75$) at 8.01 assigned to the C_2-H. The six H multiplet from 6.59 - 7.38 was due to the C_3-H, C_4-H and phenyl hydrogens. The two H triplet ($J = 7$) at 4.1 was attributed to the α-methylene of the n-hexyl substituent while the remaining hydrogens of the n-hexyl group appear as an eleven H multiplet at 0.65 - 2.11. The mass spectrum exhibited a molecular ion corresponding to $C_{17}H_{20}N_2{}^{32}S$: Mass calculated, 284.1343; found, 284.1347. These assignments are consistent with the structure 10-n-hexyl-10H-pyrido-[3,2-b][1,4]benzothiazine (CLXLV). CLXLV could arise by nucleophilic attack of n-butyllithium at the β-carbon of CLXXIIc resulting in elimination of dimethylamine. The structure of CLXLV was confirmed by an unambiguous synthesis from the reaction of CLXXIIa with sodium hydride and n-hexyl chloride.

Scheme XI

General Procedures for N-Demethylation of Amines



R = Et, Ph, Bz



CLXXIIc

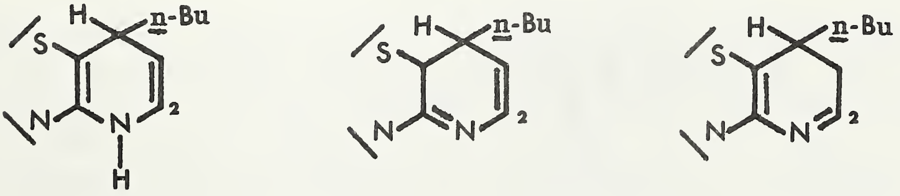
CLXLV

3.9.0.0.0 Intermediates in the reaction of 10-alkyl-10H-pyrido-[3,2-b][1,4]benzothiazine with n-butyllithium and electrophilic reagents

The reaction of 1-azaphenothiazine-n-butyllithium adducts with methyl chloroformate and diethyl chlorophosphate, as described previously, afforded 1,2-dihydropyridines CLXXVIII and 4-substituted-1-azaphenothiazines CLXXXVII in good to excellent yield. On the other hand reaction of this same adduct with such electrophiles as ethyl acetate, acetyl chloride, methanesulfonyl anhydride, trimethylsilylketene[284], and dimethyl(methylene)ammonium iodide[285] all gave a product whose nmr spectrum (δ) in the region 3 - 9 δ appeared as shown in Figure VI. Furthermore, reaction of CLXXIIb with n-butyllithium followed by quenching with water gave a product which exhibited an identical nmr spectrum. This indicated that the electrophilic reagent was not involved in the reaction. If deuterium oxide was used to quench the reaction the signals in the olefinic 5.42 - 6.24 δ region of the nmr spectrum (Figure VII) were somewhat simplified as compared

to the same region in Figure VI. It was apparent from these observations that the reaction sequence was that illustrated in Scheme XII.

Reaction of CLXXIIb with n-butyllithium gave a mixture of CLXLVIa and b which on quenching with water gave CLXXIIb and CLXLVII respectively. All efforts to obtain CLXLVII in a pure form were unsuccessful. Thin layer chromatography on silica gel or fractional crystallization of CLXXIIb resulted in aromatization of CLXLVII to CLXXXIIIb. Reduction of the imine double bond with sodium cyanoborohydride, sodium borohydride or lithium aluminum hydride was not successful. All spectral determinations were therefore made on a mixture of CLXXIIb and CLXLVII. The presence of CLXXIIb was evident from the doublet of doublets at 8.05 δ due to the C_2-H and the N-methyl singlet at 3.49 δ (Figure VI). The structure of CLXLVII was rationalized as follows. The nmr spectrum (δ) of the CLXXIIb - CLXLVII mixture exhibited the characteristic n-butyl absorption from 0.74 - 2 indicating that nucleophilic addition of the organolithium reagent had occurred. Absorptions in the ir spectrum (cm^{-1}) at 1676 and 1640 substantiated the presence of a reduced pyridyl ring. Attack by n-butyllithium at the C-4 position of CLXXIIb would give rise to three possible isomers CCa-c. The nmr spectrum of these isomers would be expected to exhibit a one H multiplet in the 8 δ region due to the C_2-H where in fact only the signal due to

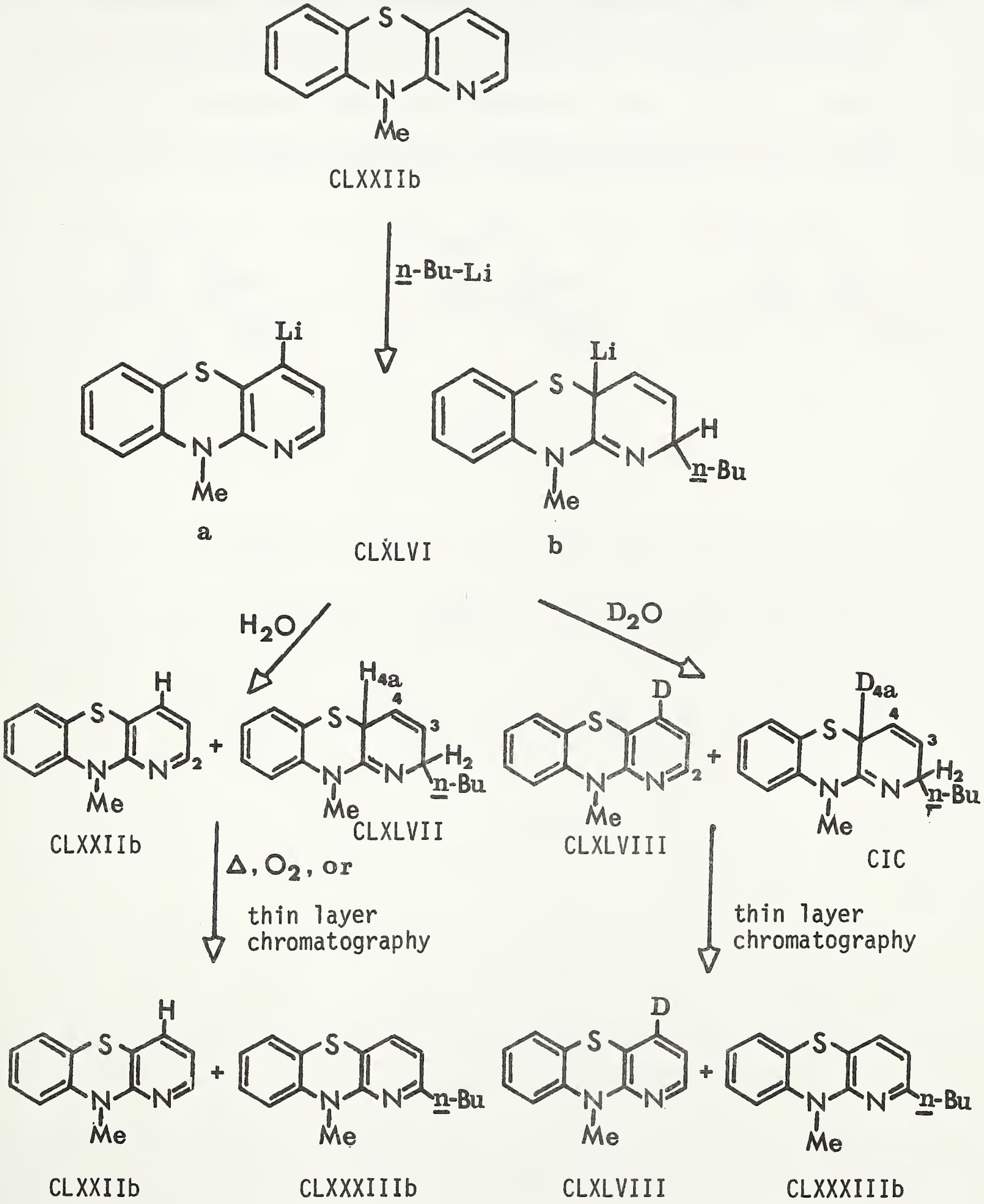


a b c

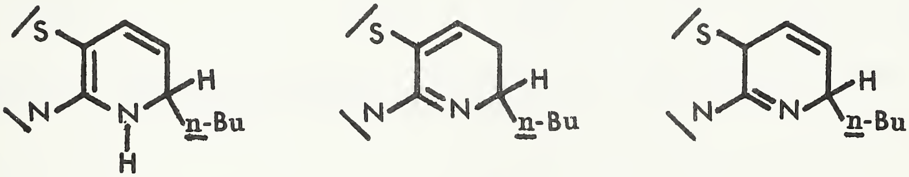
CC

Scheme XII

Intermediates in the Reaction of 10-Methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-Butyllithium



the C_2-H of CLXXIIb at 8.05 δ is observed as illustrated in Figure VI. Furthermore the chemical shifts and multiplicities of the signals in the nmr spectrum are not consistent with structures CCa-c. Attack by *n*-butyllithium must therefore have occurred as expected at the C-2 position to give one of the three possible isomers CCIa-c. Isomer CCIa can be eliminated since the ir spectrum did not exhibit an NH



a b c

CCI

absorption and treatment of the sample with deuterium oxide had no effect on the nmr spectrum. Isomer CCIb was excluded since this structure was not consistent with the signals observed in the nmr spectrum. CCIb would be expected to give a one H multiplet in the olefinic region (5-6 δ) due to the C_4-H and a two H multiplet in the region 2-2.5 δ due to the allylic hydrogens at C-3. The C_2-H signal should appear as a one H multiplet near 4 δ. On the basis of the spectral evidence the structure must be CLXLVII. The nmr spectrum (δ) in Figure VI exhibited a two H multiplet at 5.6 - 6.35 assigned to the C_3-H and C_4-H. The one H multiplets at 4.2 and 3.64 were assigned to the C_2-H and C_{4a}-H respectively. The N-10-methyl absorption appeared as a singlet at 3.41 while the *n*-butyl signal was a broad multiplet at 0.74 - 2. These assignments were confirmed by double resonance studies. Irradiation (δ) at 3.64 (C_{4a}-H) and

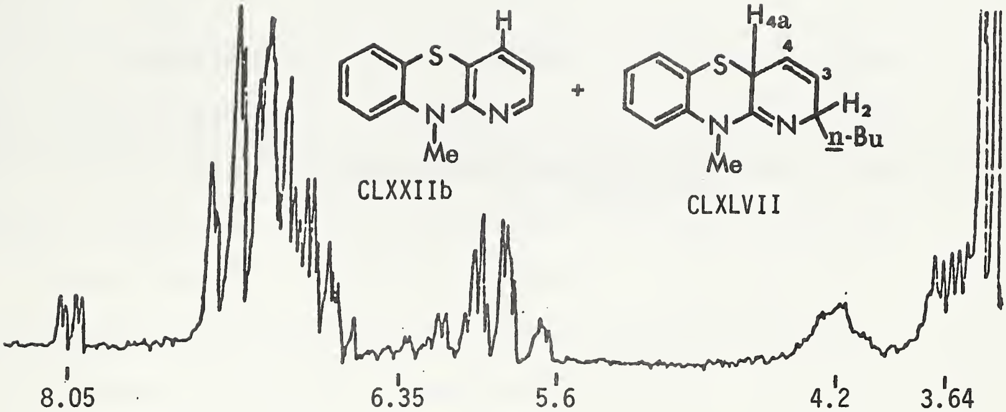


Figure VI: Reaction of 10-Methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-Butyllithium and water.

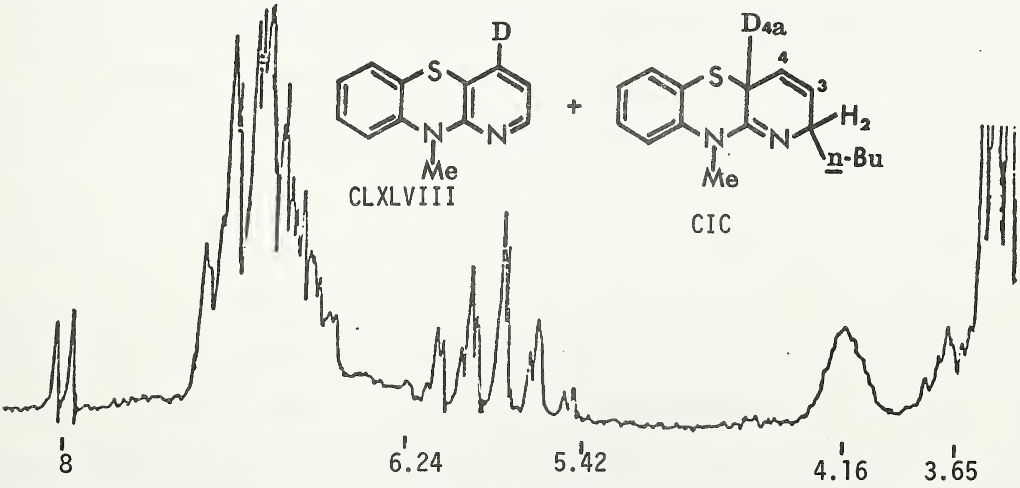


Figure VII: Reaction of 10-Methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-Butyllithium and Deuterium oxide.

4.2 (C_2-H) simplified the C_3-H, C_4-H signals as indicated in Figure VI-1 and VI-2 respectively. Irradiation at selected positions from 5.6 - 6.35 also simplified the signals due to the C_2-H and C_{4a}-H as shown in Figure VI-3. The ir spectrum (cm^{-1}) exhibited absorptions at 1676 and 1640 due to C=N and C=C stretching. These spectral assignments are consistent with the structure 2-n-butyl-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXLVII). Treatment of the CLXXIIb - CLXLVII mixture with heat or exposure to oxygen followed by thin layer chromatography on silica gel gave CLXXIIb (25.1%) and CLXXXIIIb (9.6%). The obtention of the latter product confirms that the n-butyl substituent is present at the C-2 position.

Reaction of CLXXIIb with n-butyllithium gave CLXLVIa and b which on quenching with deuterium oxide gave CLXLVIII and CIC respectively. Purification of this mixture by thin-layer chromatography on silica gel gave CLXXXIIIb and CLXLVIII in 6.7% and 13.9% yield respectively. 2-n-Butyl-4a-deutero-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine (CIC) undergoes aromatization to CLXXXIIIb during the purification process. The nmr spectrum (δ) of CLXLVIII exhibited a one H doublet ($J_{2,3}$ = 5) for the C_2-H at 8.02 while the C_3-H and phenyl hydrogens appeared as a five H multiplet at 6.68 - 7.3. The N-methyl substituent appeared as a three H singlet at 3.45. The mass spectrum exhibited a molecular ion corresponding to $C_{12}H_9N_2{}^{32}SD$: Mass calculated, 215.0626; found, 215.0620. These assignments are consistent with the structure 4-deutero-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLVIII). The structure of CIC was assigned on the basis of the nmr spectrum (δ) of a mixture of CLXLVIII and CIC (Figure VII). The doublet ($J_{2,3}$ = 5)

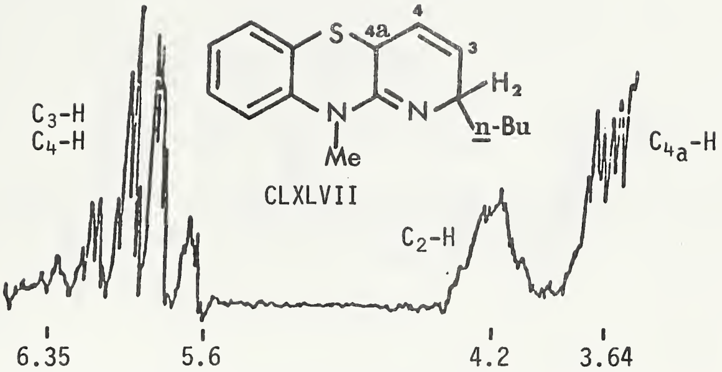


Figure VI: 3.5 δ - 6.45 δ region in the nmr spectrum of CLXLVII.

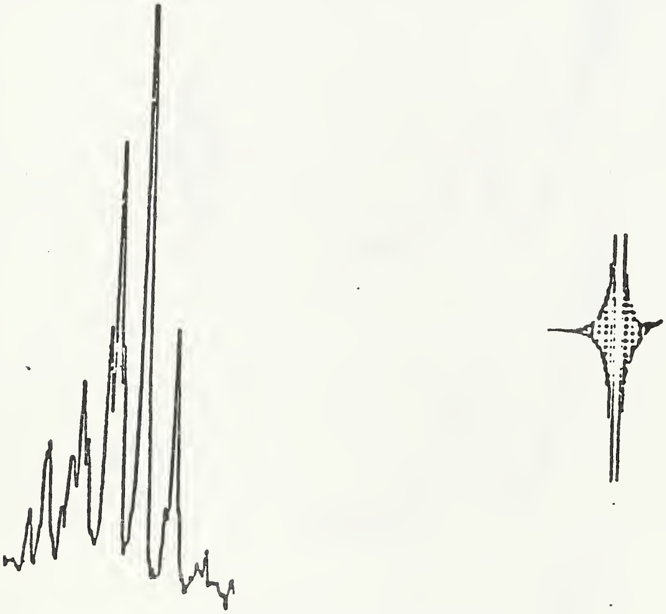


Figure VI-1: Irradiation of the C_{4a}-H of CLXLVII.

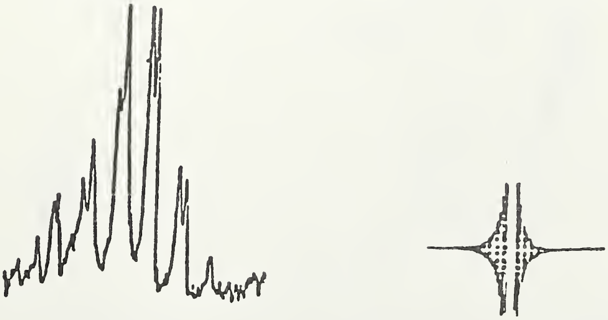


Figure VI-2: Irradiation of the C_2-H of CLXLVII.

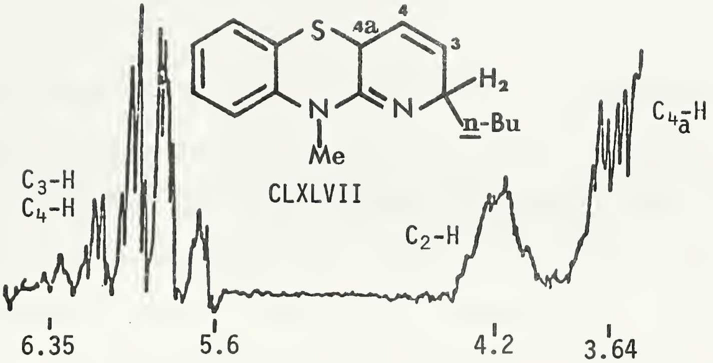


Figure VI: 3.5 δ - 6.4 δ Region in the nmr spectrum of CLXLVII.

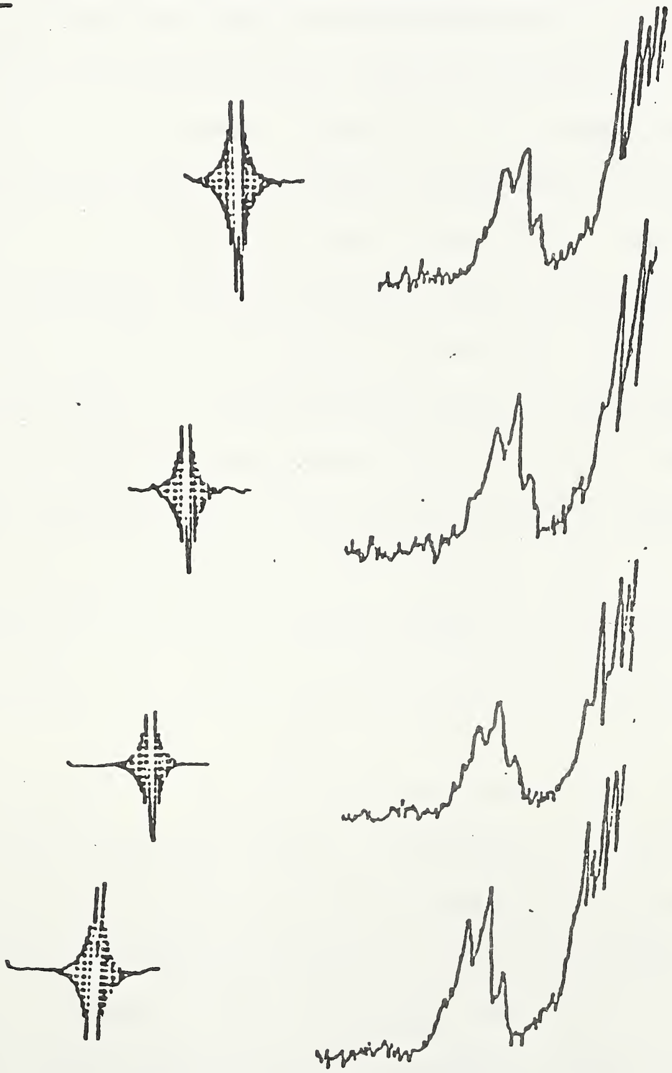
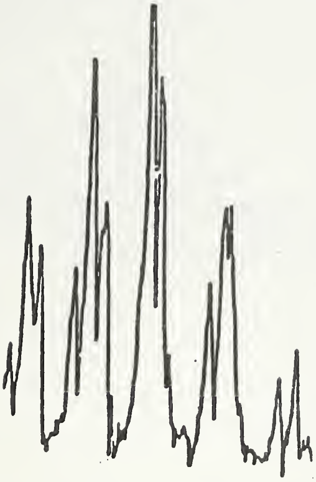


Figure VI-3: Irradiation of the C_3-H and C_4-H of CLXLVII.

at 8 is due to the C_2-H of CLXLVIII. Since the C-4a position of CIC now incorporates deuterium the C_3-H, C_4-H multiplet from 5.42 - 6.24 is simplified relative to the same protons in Figure VI. The C_2-H appears as a one H multiplet at 4.16. Irradiation of this signal results in simplification of the C_3-H, C_4-H absorption as shown in Figure VII-2. The multiplet at 3.65 in Figure VII may be an impurity or the C_{4a}-H resulting from incomplete deuteration at the C-4a position. Irradiation at this point does not change the absorption signal for the C_3-H and C_4-H as shown in Figure VII-1. In marked contrast irradiation at this position resulted in pronounced simplification of the C_3-H, C_4-H multiplet as shown in Figure VI-1. These assignments are consistent with the structure 2-n-butyl-4a-deutero-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine (CIC).

The reaction of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIId) with n-butyllithium and water or deuterium oxide gave products whose nmr spectrum was virtually identical to that observed in Figures VI and VII. This indicates that the reaction of CLXXIId with n-butyllithium probably proceeds in the same manner as that postulated for the reaction of the organolithium reagent with CLXXIIb.

The obtention of the 4a-lithio-2,4a-dihydropyridyl adduct CLXLVIb rather than the expected N-lithio-1,2-dihydropyridyl adduct CCIa may be ascribed to the ability of sulfur to stabilize an adjacent carbanion[281]. The utility of 2-lithio-1,3-dithianes[286,287] CCII as organolithium reagents is dependent on this stabilizing effect and at least one report[288] suggests the possibility of π-bonding between the sulfur



Amplification of 5.42 δ - 6.24 δ Region.

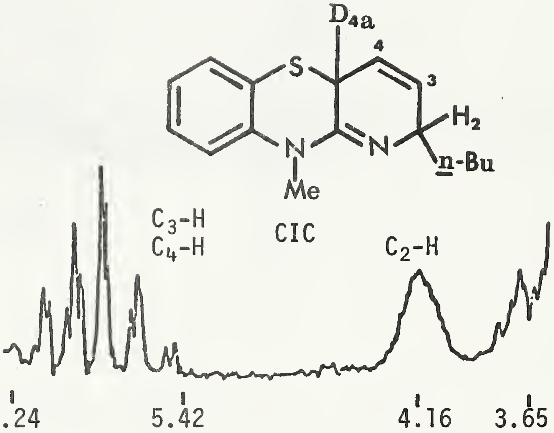
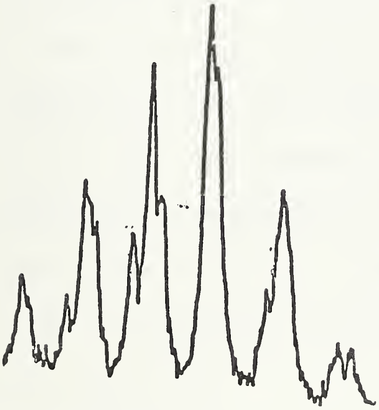


Figure VII: 3.3 δ - 6.3 δ Region in the nmr spectrum of CIC.



Amplification

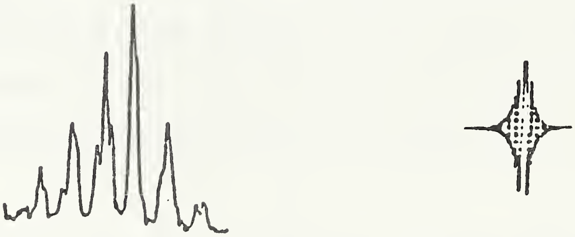
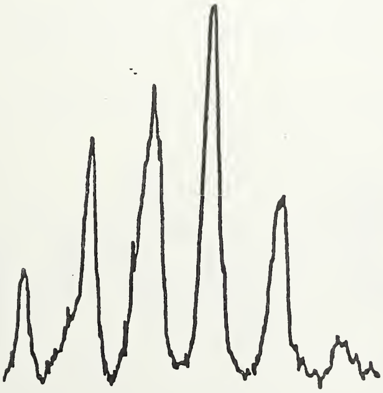


Figure VII-1: Irradiation of the C_{4a}-D of CIC.



Amplification

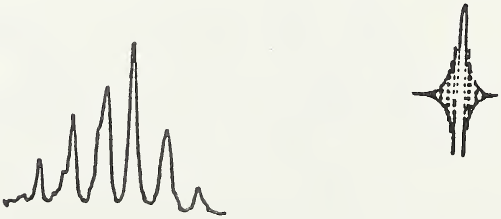
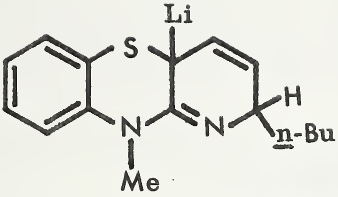
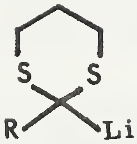


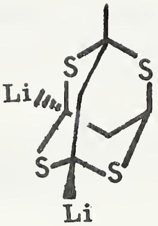
Figure VII-2: Irradiation of the C_2-H of CIC.



CLXLVIb



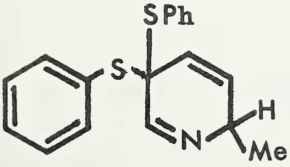
CCII



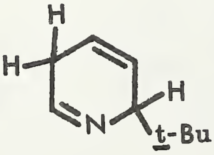
CCIII

and the bridgehead carbanions of CCIII. On the basis of these observations CLXXXVIIIb may arise as shown in Scheme XIII. Path A is unlikely since this reaction requires attack by n-butyllithium at the C-2 position of CLXXXVIIb rather than attack at the C-4 diethylphosphoryl substituent which should be more facile. Substitution at the C-4a bridgehead position as shown by Path C may be precluded due to the steric bulk of the electrophile. On the other hand attack at the ethyl group may be more favorable sterically than attack at phosphorous and therefore CLXXXVIIIb would be expected to arise *via* Path B.

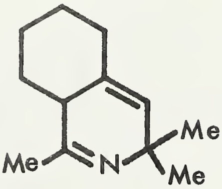
Although 2,5-dihydropyridines have been postulated as intermediates in the synthesis of 2,5-disubstituted pyridines and in the hydride reduction of pyridinium salts, their instability generally does not permit isolation. Finch and Gemenden recently reported[188] a stable



CCIV



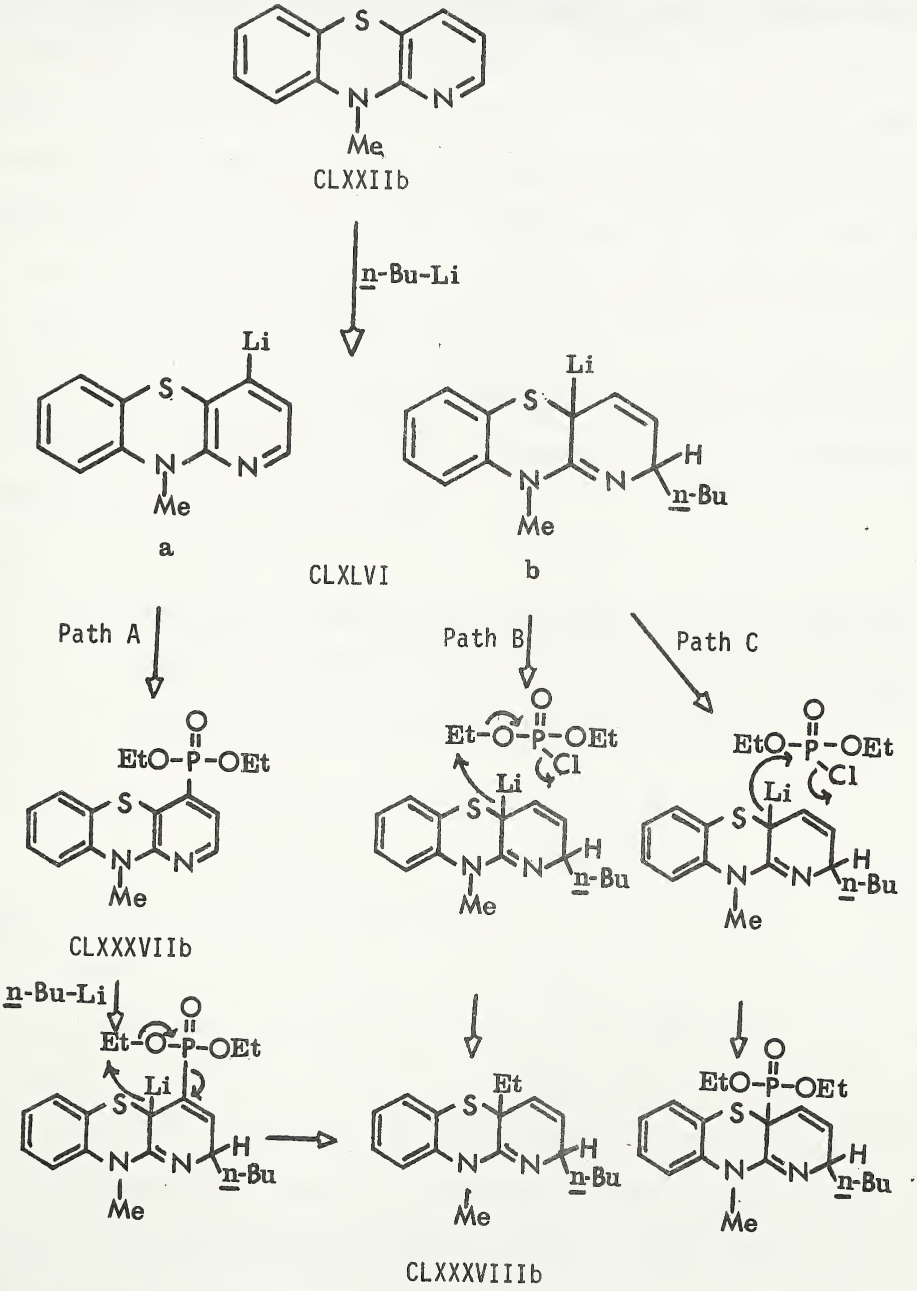
CCV



CCVI

Scheme XIII

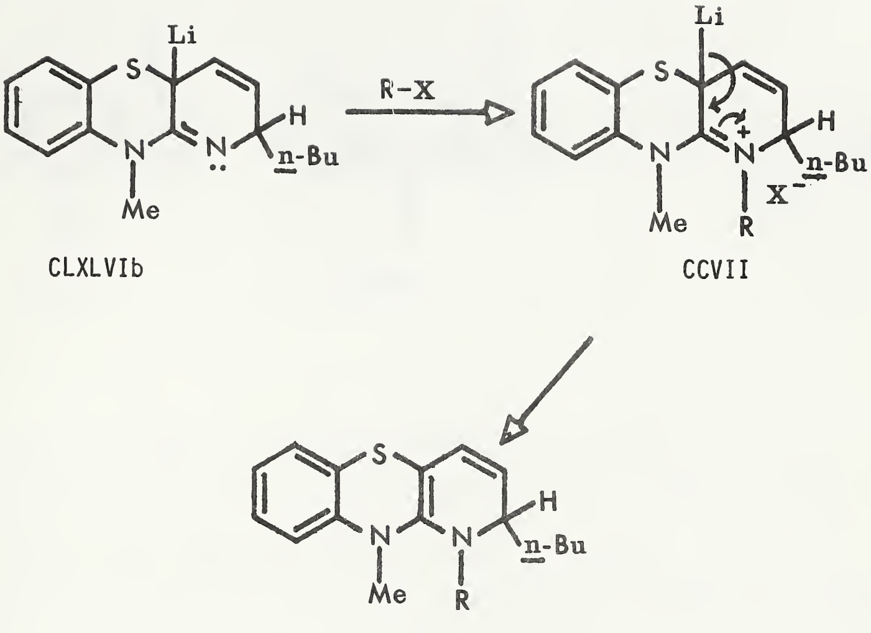
Possible Pathways for the Formation of 2-n-Butyl-4a-ethyl-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXXVIIIb)



2,5-dihydropyridine CCIV from the reaction of N-lithio-2-methyl-1,2-dihydropyridine (LXXXIa) with phenyl disulfide. The 2,5-dihydropyridine CCV has been reported[180] as an unstable product from the reaction of N-lithio-2-*t*-butyl-1,2-dihydropyridine with methanol. The ir spectrum (cm^{-1}) of CCV and CCVI[289] exhibited bands at 1675 and 1653 which were assigned to C=N stretching bands while CCIV displayed an absorption at 1634 which was not assigned. The 2,5-dihydropyridine CLXLVII exhibited an absorption of medium intensity at 1676 and one of strong intensity at 1640 while CLXXXVIIIb showed a weak band at 1677 and a strong absorption at 1631. These absorptions may be attributed to C=N and C=C stretching respectively and are in agreement with the corresponding reported absorptions for CCIV-CCVI.

3.10.0.0.0 Postulates to account for the products obtained from the reaction of 10-alkyl-10H-pyrido[3,2-b][1,4]benzothiazines with *n*-butyllithium and electrophilic reagents

Substantial evidence has been presented for the intermediacy of 4a-lithio-2-*n*-butyl-2,4a-dihydropyridine (CLXLVIb) in the acylation of 1-azaphenothiazine-*n*-butyllithium adducts. It could be proposed that any electrophile which is incapable of forming an iminium intermediate CCVII will not react further to afford a 1,2-dihydropyridine CCVIII. The necessary formation of CCVII would explain the apparent inertness of such powerful electrophiles as trimethylsilylketene[284] and dimethyl-(methylene)ammonium iodide[285] on attempted reaction with the adduct CLXLVIb. These electrophilic reagents as well as ethyl acetate and methanesulfonyl anhydride do not afford 1,2-dihydropyridines CLXXVIII



CLXLVIb

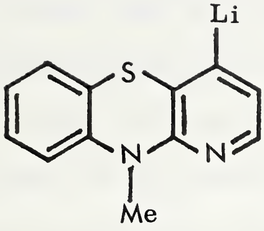
CCVII

CCVIII

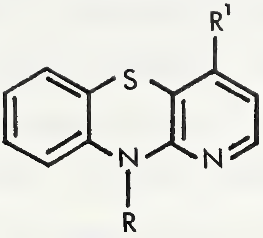
but rather 2,4a-dihydropyridines CLXLVII. Although the intermediacy of CCVII provides a mechanistically plausible pathway to CCVIII certain observations suggest that other, as yet unexplained, factors are also involved, viz;

1. Reaction of the CLXXIIb-n-butyllithium adduct with acetyl chloride and methanesulfonyl anhydride do not afford any characterizable product other than unreacted starting material CLXXIIb. This is puzzling since both reagents should be capable of forming the intermediate CCVII.

2. Examination of data presented in Table IX indicates that 4-substituted-1-aza-phenothiazines CLXXXVII expected from acylation of intermediate CLXLVIa are not produced. The absence of 1,2-dihydropyridines CCVIII in the reaction of CLXXIIb-n-butyllithium adducts



CLXLVIa



CLXXXVII

R = Me

R^1 = $COCH_3$, $CH_2N(Me)_2$,
$COCH_2Si(Me)_3$,
SO_2Me

with such electrophiles as dimethyl(methylene)ammonium iodide and trimethylsilylketene was previously rationalized in terms of their inability to form the iminium species CCVII. However, there is no apparent explanation as to why the corresponding 4-substituted compound CLXXXVII is not obtained with these electrophilic reagents.

3. Analysis of the results shown in Table IX also indicates that the 1-aza-phenothiazines CLXXII in which the N-10 substituent was methyl (CLXXIIb), 3-dimethylaminopropyl (CLXXIId) and 2-dimethylaminopropyl (CLXXIIe) gave the expected 1,2-dihydropyridyl products arising from reaction at the N-1 nitrogen. The 1-azaphenothiazines CLXXII in which the N-10 substituent was 2-dimethylaminoethyl (CLXXIIc) or 1-methyl-2-dimethylaminoethyl (CLXXIIf) afforded only products resulting from reaction at the N-10 side chain.

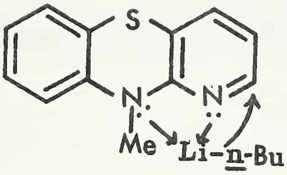
Earlier in the discussion it was proposed that the species CLXLII was involved in the formation of 4-substituted-1-azaphenothiazines CLXXXVII. While the proposed complex CLXLII has two nitrogens available for complexing with n-butyllithium the 1-azaphenothiazines with an N-10 dimethylaminoalkyl substituent have three nitrogens. The following postulates are presented on the basis of the products

isolated from the reaction of 1-azaphenothiazines CLXXIIb-f with n-butyllithium and electrophilic reagents. The complex CLXLII shown in Figure VIII has been proposed to explain the enhanced basic properties of n-butyllithium. If such a complex is involved the C-2 position of the pyridyl ring should be more susceptible to nucleophilic attack since the pyridyl nitrogen would attain some positive character. Furthermore, complexation would orient the n-butyl group of n-butyllithium such that nucleophilic attack at the C-2 position is facilitated.

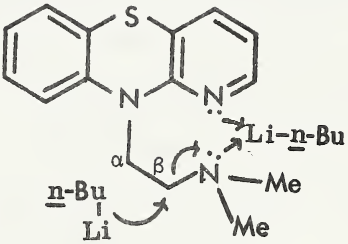
Reaction of 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIc) with n-butyllithium and methyl chloroformate affords CLXLIV for which a mechanism to explain its formation has been proposed. The reaction of CLXXIIc with n-butyllithium alone afforded CLXLV presumably as a result of attack by n-butyllithium at the β-carbon of the side chain of CLXXIIc with loss of dimethylamine. The N-10 side chain nitrogen which is more basic than N-10 may in conjunction with the pyridyl nitrogen complex n-butyllithium as shown by CCIX in Figure VIII. Complexation with these nitrogen atoms may be sterically more favorable than complexation with the peri-N-1 and N-10 nitrogens as shown by CLXLII. If this is true then the N-10 side chain nitrogen would attain some positive character and the possibility of eliminating a stable molecule (dimethylamine) facilitates attack by n-butyllithium at the β-carbon. Complexation would also make the C-2 position more susceptible to nucleophilic attack since the pyridyl nitrogen would also attain some positive character. However, the only product isolated CLXLV was the result of reaction at the side chain and therefore this type of attack must be more favorable.

Figure VIII

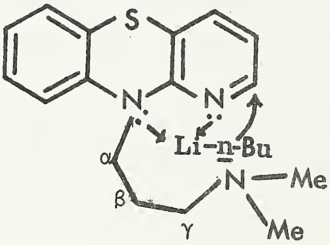
Possible Complexes from the Interaction of
1-Azaphenothiazines with *n*-Butyllithium



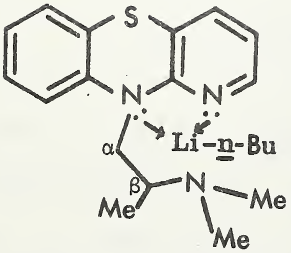
CLXLII



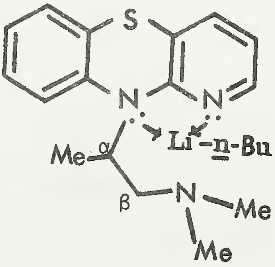
CCIX



CCX



CCXI



CCXII

Furthermore, if the complex shown by CCIX is possible the n-butyl group of n-butyllithium may be oriented such that it is too far from the C-2 position to permit attack at that site.

The reaction of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIId) with n-butyllithium and electrophilic reagents proceeds such that the only products isolated are those arising from reaction at the pyridine N-1 nitrogen. This suggests that the N-1 and N-10 nitrogens may be involved in complexation with n-butyllithium as shown by CCX in Figure VIII. If such a complex is present nucleophilic attack at the C-2 position would be facilitated. On the other hand, if the N-1 and the N-10 side chain nitrogens are involved in complexation one might expect attack by n-butyllithium at the γ-carbon with elimination of dimethylamine. Since no product arising from such attack was observed it appears that the three carbon side chain may be too long to permit the type of complexation shown by CCIX.

The reaction of 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIe) with n-butyllithium and electrophilic reagents proceeds such that the only products isolated are those arising from reaction at the pyridine N-1 nitrogen. It might be expected that the N-1 and N-10 side chain nitrogens would be involved in complexation since we again have a two carbon side chain which would give a complex such as CCIX. It has been suggested[303] that in the phenothiazine series CLXXVI there is steric repulsion between a methyl substituent R^1 at the β-position and the 1,9-peri-hydrogens. By analogy we might expect that a similar repulsion exists between the β-methyl substituent and the peri-C-9 hydrogen and the peri-N-1 lone electron pair of

CLXXIIe. If this is true then complexation of the type shown by CCIX is probably not possible due to steric reasons. Complexation with n-butyllithium might then occur with the N-1 and N-10 nitrogens as shown by CCXI in Figure VIII. Such a complex would then facilitate attack at the C-2 position.

The reaction of 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido-[3,2-b][1,4]benzothiazine (CLXXIIf) with n-butyllithium and methyl chloroformate afforded CLXXIIa presumably as a result of attack by n-butyllithium at the α-carbon of CLXXIIf. Since steric repulsion is present between the β-methyl and the *peri*-positions of CLXXIIe we might expect similar but more pronounced interactions in CLXXIIf since the methyl substituent is at the α-position. If this is true then a complex of the type shown by CCIX is not possible whereas that shown by CCXII in Figure VIII might still be obtained. Such a complex would confer slight positive character to the N-10 nitrogen facilitating nucleophilic attack by n-butyllithium at the α-position. Attack at this site would also eliminate a stable molecule, CLXXIIa, as well as relieve the steric repulsion between the α-methyl substituent and the *peri*-positions. On the other hand, complex CCXII would also activate the C-2 position towards nucleophilic attack by confering slight positive character to the N-1 nitrogen. No product arising from reaction at the pyridyl N-1 nitrogen was obtained indicating that nucleophilic attack on the side chain is a more favorable process.

It must be stressed that the preceding postulates are presented in an effort to rationalize the dependence of the reaction products which are obtained to the nature of the N-10 substituent of 1-azaphenothiazines CLXXII.

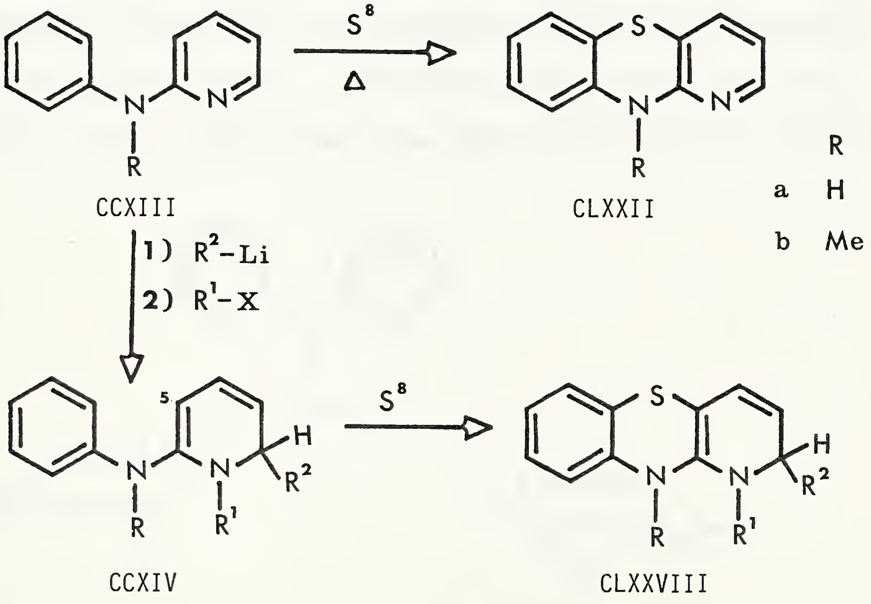
It is recognized that in the absence of concrete evidence supporting the existence of the complexes such as CLXLII and CCIX-CCXII these postulates are at best quite tenuous. Furthermore they virtually ignore a variety of other possible complicating factors. Complexation between n-butyllithium and 1-azaphenothiazines CLXXII has been shown in CLXLII and CCIX-CCXII as involving the N-1 and N-10 nitrogens or the N-1 and N-10 side chain nitrogens. There is no reason why complexation might not also involve the N-10 and N-10 side chain nitrogens. In fact complexation may be inter- rather than intramolecular or may occur at individual nitrogens rather than requiring a nitrogen pair. On the other hand complexation may not occur to any significant extent.

No allowance has been made for the conformation of the 1-azaphenothiazine system CLXXII and its effect on chemical reactivity. Studies in the phenothiazine series CLXXVI suggest that the two phenyl rings are at right angles to one another[304]. If the 1-azaphenothiazine molecule CLXXI is similarly non-planar we might expect this conformation to influence the reaction course. Similarly no consideration is given to the possible inversion of the N-10 nitrogen.

It should be pointed out however that while the reaction of CLXXIIb or d with n-butyllithium and water gave a product(s) whose nmr spectrum is shown in Figure VI the same reaction with CLXXIIc gave no evidence for such products in the nmr spectrum. This at least indicates that while CLXXIIb and d undergo reaction at the pyridyl N-1 nitrogen via the same type of intermediates CLXLVIa and b no such adducts have been detected which would suggest a similar reaction at the pyridine N-1 nitrogen of CLXXIIc.

3.11.0.0.0 Synthesis of 2-anilinopyridines

In view of the wide variety of products obtained from the reaction of 1-azaphenothiazines CLXXII with *n*-butyllithium and electrophilic reagents CLXXXVI it was considered desirable to find alternative routes to the 1,2-dihydropyridine derivatives CLXXVIII. One possible alternative involves the preparation of the 1-azaphenothiazine skeleton CLXXII from the reaction of 2-anilinopyridine CCXIIIa with elemental sulfur and iodine[244].



Reaction of CCXIII with an organolithium reagent R^2-Li and an electrophile R^1-X could be expected to afford the 2-anilino-1,2-dihydropyridine CCXIV as the sole or major product. Reaction of CCXIV with elemental sulfur would then afford the desired 1,2-dihydropyridine CLXXVIII. If successful this synthetic route to CLXXVIII would eliminate the variety of by-products obtained from the reaction of

[illegible]

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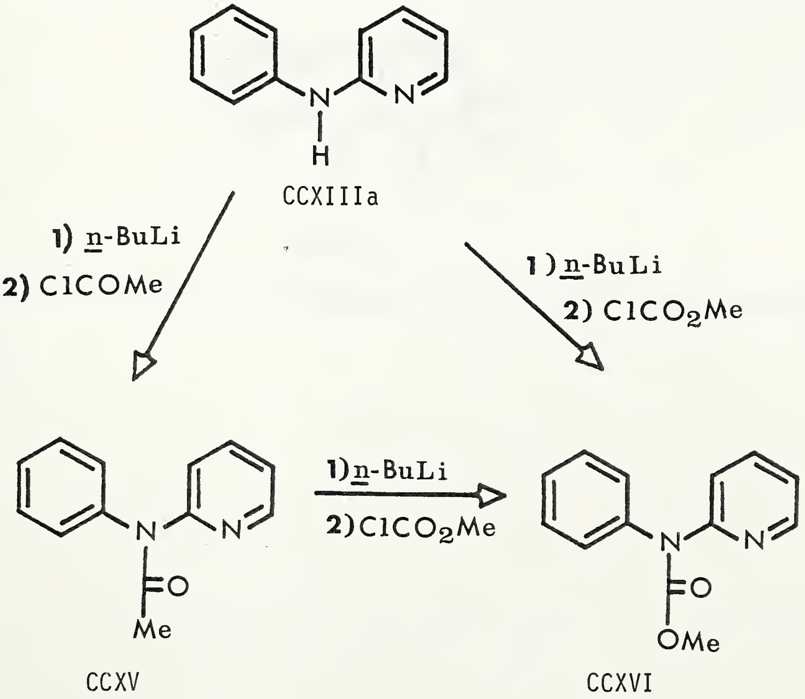
1-azaphenothiazines CLXXII with n-butyllithium and electrophiles. It was further expected that the electron rich C-5 position in the 1,2-dihydropyridine ring of CCXIV would facilitate ring closure with elemental sulfur. If this were found to be the case the prohibitive temperatures required for the conversion of CCXIII to CLXXII might then be avoided.

2-Anilinopyridine[245] (CCXIIIa) and 2-(N-methylanilino)-pyridine (CCXIIIb) were prepared according to a published procedure or its variation. The reaction of CCXIIIb with n-butyllithium and methyl chloroformate afforded 39% starting material CCXIIIb and intractable tar. The reaction of CCXIIIa with excess n-butyllithium and acetyl chloride or methyl chloroformate gave CCXV or CCXVI in 91.5% and 93.2%



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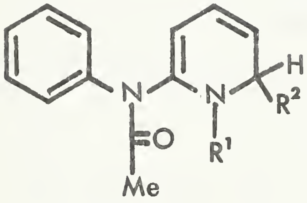
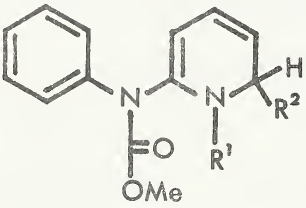
yield respectively. Treatment of CCXV with n-butyllithium and methyl chloroformate gave CCXVI in 79.2% yield while the reaction of CCXVI with the same reagents gave starting material CCXVI almost quantitatively.

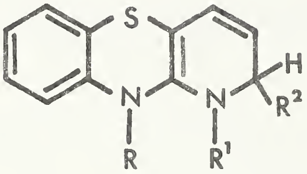
Further studies are now in progress to elaborate the pyridyl ring of CCXV and CCXVI to give CCXVII and CCXVIII using other methods of generating 1,2-dihydropyridyl derivatives[144,158]. These derivatives will then be subjected to elemental sulfur to effect cyclization to CLXXVIII.



CCXVII



CCXVIII



CLXXVIII

4.0.0.0.0 Broad Spectrum Pharmacological Screening

Ten selected compounds viz: CXXXIXd, CXXXIXf, CXXXIXg, CXXXIXh, CXXXIXi, CXXXIXj, CXXXIXk and the mixture of isomers CXXXIXa and CXLa, CXXXIXb and CXLb and CLVIIa and CLVIIIa have been evaluated by Dr. E.A. Swinyard (University of Utah) for antiepileptic and neurotoxic activity.

Each compound was administered via the intraperitoneal route and tested in the Maximal Electroshock and Subcutaneous Pentylenetetrazol (Metrazol) Seizure models and the 6 RPM Rotorod Ataxia test in mice over the dose range 200 - 1600 mg/kg body weight. Electroshock was applied at 1, 2 and 4 hours after treatment while Metrazol was injected 1 hour after treatment.

Although these compounds were generally non-toxic even at high doses (TD_{50} > 1600 mg/kg) they were not effective in the maximal electroshock and metrazol models (ED_{50} > 1600 mg/kg). Compound CXXXIXj caused ataxia in those mice injected with 800 mg/kg while the 1600 mg/kg dose was very toxic. The mixture of isomers CXXXIXb and CXLb appeared to potentiate the action of metrazol although it was non-toxic at all dose levels. Compound CXXXIXh exhibited depressant activity but did not control electrically or chemically induced seizures. Compound CXXXIXk was found to give a very light protection against electroshock when administered at the 1600 mg/kg dose level 4 hours after administration.

The broad spectrum pharmacological screening of compounds LXXXIVb, CXIXb, XXXIXc, CXXXIXh and the isomeric mixture CXXXIXa and CXLa has been completed.

The screening is conducted under a "Screening Program for New Drug Type Discoveries" under an agreement between Canadian Patents and Developments Limited and Bio-Research Laboratories Limited.

Prior to initiation of the broad spectrum pharmacological screen the test compound is administered to mice and its behaviour is closely observed to establish a neuropharmacological profile. The compound is then subjected to tests designed to detect specific activity of the following types: analgesic, antidepressant, cardiovascular, contraceptive, anti-inflammatory, hypoglycemic, antihistaminic, anti-anaphylactic, antimicrobial, antiprotozoal and inhibition of the enzyme histidine decarboxylase.

The neuropharmacological profile of compound CXXXIXh was determined after intraperitoneal injection to Swiss Albino mice. Compound CXXXIXh was found to exhibit a depressant effect.

Hypoglycemic effects were determined by oral administration of the compound to Sprague-Dawley rats. Compound CXXXIXh and a mixture of the isomers CXXXIXa and CXLa caused a slight reduction in the blood glucose concentration.

The in vitro antimicrobial activity of compounds LXXXIVb, CXIXb, XXXIXc, CXXXIXh and a mixture of the isomers CXXXIXa and CXLa was determined using bacteria, fungi, yeast and protozoa. Minimal Inhibitory Concentrations (MIC) in micrograms of compound per millilitre of media were interpreted as follows: bacteria; < 100 μg/ml (active), 100-500 μg/ml (slightly active), > 500 μg/ml (inactive), fungi and yeast; < 10 μg/ml (active), 10-500 μg/ml (slightly active) and > 500 μg/ml (inactive), protozoa; trichomonas, > 50 μg/ml (inactive), entamoeba, > 10 μg/ml (inactive).

All compounds were inactive against the bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhimurium*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus faecalis* and *Bacillus subtilis*.

Antifungal activity tests were conducted against *Trichophyton mentagrophytes*, *Microsporum gypseum*, *Aspergillus niger*, *Candida albicans* and *Saccharomyces carbargensis*. Compounds LXXXIVb, CXIXb and XXXIXc were found to be slightly active against *Trichophyton mentagrophytes* and *Microsporum gypseum*.

All compounds were found to be inactive against the protozoa *Trichomonas foetus* and *Entamoeba histolytica*.

The pharmacological profile of compounds CLXXVIIIa and CLXXVIIIe is currently being determined.

5.0.0.0 Experimental

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Infrared spectra (in potassium bromide unless otherwise noted) were taken on a Unicam SP-1000 or Perkin-Elmer 267 spectrometer. Nmr spectra were determined for solutions of deuterochloroform (unless otherwise noted) using TMS as internal standard with a Varian A-60, EM-360, HA-100 or 220 spectrometer. Coupling constants are given in Hertz (Hz) in all cases. Mass spectra were measured with an AEI-MS-9 or MS-50 mass spectrometer and the exact mass measurements are used in lieu of elemental analyses. Gas chromatography was performed on a Hewlett-Packard 5710A dual column chromatograph.

5.1.0.0.0 Reagents and solvents

n-Butyllithium (1.75 - 2.5 molar in *n*-hexane solution) was obtained from Aldrich Chemical Co., Inc. or from Alfa Products and was assayed prior to use following the method of H. Gilman and A.H. Haubein[237]. The chemical analysis of organolithium compounds has been reviewed[249]. Methyllithium (1.5 molar in ether solution) was obtained from Alfa Products and assayed[237] prior to use. Phenyllithium was prepared according to the procedure outlined in Section 5.1.1.0.0.

N-Acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa)[190] *N*-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXc)[190], *N*-benzoyl-2-phenyl-1,2-dihydropyridine (XXXIXd)[190], *N*-methoxycarbonyl-1,2-dihydropyridine

(LV)[144] and N-methanesulfonyl-1,2-dihydropyridine (CXXXVII)[243] were prepared according to published procedures. 4-Phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa) was prepared by nitrogen tetroxide[238] oxidation of 4-phenyl-1,2,4-triazolidine-3,5-dione prepared using the procedure of G. Zinner and W. Deucker[239]. This was purified by sublimation (100°/0.2 mm) to give CXXXVIIIa, mp 173°-182° (decomp.) [reported[248] 160-180 (decomp.)]. 4-Ethyl-1,2,4-triazoline-3,5-dione (CXXXVIIIb) was similarly prepared. 1,2,4-Triazoline-3,5-dione (CXXXVIIIc) was prepared by the nitrogen tetroxide oxidation of urazole obtained from Aldrich Chemical Co., Inc.

4,4-Diethylpyrazoline-3,5-dione (CLIV) was obtained from the nitrogen tetroxide oxidation of 4,4-diethylpyrazolidine-3,5-dione, mp 264-5° (from water); reported[240], mp 266-7°. Lithium diisopropylamide was prepared using the procedure of R.J. Cregge and co-workers[241]. 10H-Pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) was obtained from Aldrich Chemical Co., Inc. and was recrystallized from hexanes (bp 68.4°-68.9°)-benzene (2:1 v/v), mp 113-4°.

10-(3-Dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine hydrochloride monohydrate (Tolnate) was obtained from Smith, Kline and French Labs., Ltd. Anhydrous ether and tetrahydrofuran were obtained by distillation from lithium aluminum hydride or from benzophenone ketyl[242]. Anhydrous dichloromethane was predried (calcium chloride) and distilled from calcium hydride. Anhydrous toluene was predried (calcium hydride) and distilled from sodium. Silica gel (J.T. Baker Chemical Co., 40-140 mesh) or neutral alumina, Brockman activity 1 (Fisher Scientific Co., 80-200 mesh)

were used for column chromatography. Kieselgel silica gel DF-5 (Camag) was used for preparative thin layer chromatography. Preparative thin layer chromatography plates were 20x20 cm (unless otherwise noted) and the silica gel was 0.75 mm (unless otherwise noted) in thickness. Silica gel fractions were extracted with methanol. Temperatures of 0° and -77° were obtained with ice-water and dry ice-acetone baths respectively. Reactions were carried out in glassware which was oven-dried overnight at 120° and cooled to room temperature by flushing with nitrogen or argon gas. Inert gases (nitrogen and argon) were dried by successive passage through sulfuric acid, potassium hydroxide and calcium chloride.

5.1.1.0.0 Preparation of phenyllithium

Bromobenzene (15.7 g, 0.1 mol) in anhydrous ether (25 ml) was added dropwise to a vigorously stirred suspension of lithium metal (1.53 g, 0.22 mol) in anhydrous ether (175 ml) at 0° under an atmosphere of nitrogen. The solution was allowed to warm to room temperature and then stand at room temperature overnight under a positive nitrogen atmosphere. A black precipitate settles out leaving phenyllithium as a light yellow solution which was assayed using the procedure of H. Gilman and A.H. Haubein[237].

5.2.0.0.0 The generation of N-lithio-2-phenyl-1,2-dihydropyridine and subsequent reaction with electrophilic reagents

General Procedure: Pyridine (7.9 g, 0.1 mol) in anhydrous ether (10 ml) was added dropwise to a stirred solution of phenyllithium (8.4 g, 0.1 mol) in anhydrous ether (200 ml) at 0° under a dry nitrogen atmosphere. Upon standing overnight at 0° N-lithio-2-phenyl-1,2-dihydropyridine (LXXXIc) was obtained as a yellow crystalline solid which was washed with anhydrous ether (2x30 ml), dissolved in anhydrous tetrahydrofuran (50-60 ml), and assayed using the procedure of H. Gilman and A.H. Haubein[237]. The dark brown solution of LXXXIc was cooled to -77° and the appropriate electrophile (0.1 mol) in anhydrous tetrahydrofuran (10 ml) was added dropwise with stirring. The resulting dark yellow solution was stirred at -77° for 1 hr and then allowed to warm to room temperature over a 1 hr period. Water (50-100 ml) was added and the reaction products were isolated as described in reported procedures[189,190].

5.3.0.0.0 The generation of N-lithio-2-alkyl-1,2-dihydropyridine and subsequent reaction with electrophilic reagents

General Procedure: In a dry nitrogen atmosphere pyridine (3.01 g, 38 mmol) in anhydrous ether (10 ml) was added dropwise to a stirred solution of alkyllithium (38 mmol) in anhydrous ether (50 ml) at 0°. The resulting reddish-brown solution of N-lithio-2-alkyl-1,2-dihydropyridine was stirred at 0° for 1 hr, cooled to -77°, and the appropriate electrophile (38 mmol) in anhydrous ether

(10 ml) was added dropwise with stirring. The resulting dark yellow solution was stirred at -77° for 1 hr and then allowed to warm to room temperature over a 1 hr period. Water (50-75 ml) was added and the reaction products were isolated as described in individual reactions.

5.3.1.0.0 Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with methyl chloroformate

In a dry nitrogen atmosphere methyl chloroformate (2.6 g, 27.5 mmol) in anhydrous ether (10 ml) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) (3.93 g, 27.5 mmol prepared according to the procedure outlined in Section 5.3.0.0.0) in anhydrous ether (60 ml) at -77°. The resulting clear yellow solution was allowed to warm to room temperature over a 1 hr period and successively treated with water (75 ml), 18% HCl (4x50 ml) and water (2x50 ml). The ether phase was separated, dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil (4.74 g) which was chromatographed on a 2.5x20 cm neutral alumina column. Elution with petroleum ether (bp 35-60°)-benzene (300 ml) (1:1 v/v) and petroleum ether-benzene (200 ml) (1:3 v/v) gave N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIVb) as a light yellow oil (0.821 g, 15.3%). ν_{max} (film) (cm^{-1}): 1718 (C=O), 1645, 1580 (C=C); nmr δ: 6.72 [1H, d($J_{5,6}$ = 7.5), C_6-H], 5.95 [1H, d($J_{3,4}$ = 8.75) of d($J_{4,5}$ = 5.5), C_4-H], 5.68 [1H, d($J_{2,3}$ = 5), C_3-H], 5.26 (1H, m, C_5-H), 4.75 (1H, m, C_2-H), 3.78 (3H, s, OMe), 1.9-0.7 (9H, m, n-Bu); mass calculated for $C_{11}H_{17}NO_2$, 195.1259; found, 195.1266.

Further elution with benzene (400 ml) and then benzene-ether (100 ml) (1:1 v/v) gave 1,5-dimethoxycarbonyl-2-n-butyl-1,2-dihydropyridine (CXIXb) as a light yellow oil (1.148 g, 33%). ν_{max} (film) (cm^{-1}): 1734, 1712 (C=O), 1642, 1590 (C=C); nmr δ: (1H, s, C_6-H), 6.46 [1H, d($J_{3,4}$ = 9.75), C_4-H], 5.62 [1H, d($J_{3,4}$ = 9.75) of d($J_{2,3}$ = 5.5) of d($J_{3,6}$ = 1), C_3-H], 4.78 [1H, d($J_{2,3}$ = 5.5), C_2-H], 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 1.65-0.65 (9H, m, n-Bu); mass calculated for $C_{13}H_{19}NO_4$, 253.1314; found, 253.1310. The reaction was also quantitated prior to treatment with 18% HCl. Vpc analysis on a 6 ft x 1/4 in column packed with 3% OV-17 on Chrom W (80-100 mesh) with a He flow rate of 50 ml/min and a column temperature of 155° gave 2-n-butylpyridine (CXXIb) identical (ir) with an authentic sample (5%, retention time 1 min). A column temperature of 205° gave N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIVb) (43%, retention time 1.12 min) and 1,5-dimethoxycarbonyl-2-n-butyl-1,2-dihydropyridine (CXIXb) (25%, retention time 3.25 min). When the reaction was repeated using 5 equivalents of methyl chloroformate followed by vpc analysis as described above CXXIb (6%), LXXXIVb (35%) and CXIXb (34%) were obtained.

5.3.2.0.0 Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with 3-ethoxycarbonylpyridine

In a dry nitrogen atmosphere 3-ethoxycarbonylpyridine (CXVIIIc) (1.51 g, 10 mmol) in anhydrous ether (5 ml) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) (1.43 g, 10 mmol, prepared according to the procedure

outlined in section 5.3.0.0.0) in anhydrous ether (60 ml) at room temperature. The resulting rusty-brown suspension was stirred for a further 1 hr and water (90 ml) was added. Extraction with ether (6x30 ml), drying (Na_2SO_4) and evaporation of the solvent in vacuo gave a red oil (2.455 g) of which 0.5 g was subjected to preparative thin-layer chromatography on three (20x40 cm) silica gel plates using ether-methanol (9:1 v/v) as the development solvent.

Extraction of the silica gel fraction (Rf 0.42) gave 2-*n*-butyl-5-(3'-pyridylcarbonyl)-1,2-dihydropyridine (CXXc) as a bright yellow oil (0.195 g, 39.6%). ν_{max} (film) (cm^{-1}): 3260 (NH), 1652 (C=O), 1580 (C=C); nmr δ: 8.58 [1H, d($J_{2',4'}$ = 2), $C_{2'}$-H], 8.53 [1H, d($J_{5',6'}$ = 5) of d($J_{4',6'}$ = 2), $C_{6'}$-H], 7.72 (1H, d($J_{4',5'}$ = 8.5) of t($J_{4',6'}$ = $J_{2',4'}$ = 2), $C_{4'}$-H], 7.4-6.94 (3H, m, $C_{5'}$-H, C_6-H, NH, exchanges with deuterium oxide), 6.54 [1H, d($J_{3,4}$ = 10), C_4-H], 5.15 [1H, d($J_{3,4}$ = 10), C_3-H], 4.29 (1H, m, C_2-H), 1.77-0.66 (9H, m, *n*-Bu). After D_2O exchange the C_3-H multiplet appears as a d($J_{3,4}$ = 10) of d($J_{2,3}$ = 3.5); mass calculated for $C_{15}H_{18}N_2O$, 242.1415; found, 242.1414. Extraction of the silica gel fraction (Rf 1) gave a dark yellow oil which was rechromatographed on one (20x40 cm) silica gel plate using ether-methanol (20:1 v/v) as the development solvent. This gave three fractions (Rf 1), (Rf 0.95), and (Rf 0.76). Extraction of the silica gel fraction (Rf 1) gave 2-*n*-butylpyridine (CXXIc) as a light yellow oil (0.022 g, 8%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (Rf 0.95) gave 3-ethoxycarbonylpyridine (CXVIIIc) as a colorless oil (0.083 g, 27%) identical (nmr) with an authentic sample. Extraction of the

silica gel fraction (Rf 0.76) gave 2-n-butyl-5-(3'-pyridylcarbonyl)-pyridine (LXXXVc) as a very light yellow oil (0.013 g, 2.7%). ν_{max} (film) (cm^{-1}): 1670 (C=O); nmr δ: 9.05-8.7 (3H, m, C_2'-H, C_6'-H, C_6-H), 8.24-7.92 (2H, m, C_4'-H, C_4-H), 7.59-7.2 (2H, m, C_5'-H, C_3-H), 2.89 [2H, t($J_{CH_2-CH_2}$ = 7)$\underline{H_2}$...

5.3.3.0.0 Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with 4-methoxycarbonylpyridine

In a dry nitrogen atmosphere 4-methoxycarbonylpyridine (CXVIIId) (2.74 g, 20 mmol) in anhydrous ether (10 ml) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXId) (2.86 g, 20 mmol, prepared according to the procedure outlined in section 5.3.0.0.0) in anhydrous ether (60 ml) at room temperature. The resulting rusty-brown suspension was stirred for a further 0.5 hr and water (100 ml) was added. Extraction with ether (6x100 ml) drying (Na_2SO_4) and evaporation of the solvent in vacuo gave a red oil (4.49 g) of which 0.7 g was subjected to preparative thin-layer chromatography on six (20x40 cm) silica gel plates using ether-methanol (15:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.21) gave 2-n-butyl-5-(4'-pyridylcarbonyl)-1,2-dihydropyridine (CXXd) as a bright yellow oil (0.358 g, 47.4%). ν_{max} (film) (cm^{-1}): 3240 (NH), 1650 (C=O), 1567 (C=C); nmr δ: 8.62-8.4 (2H, m, C_2'-H, C_6'-H), 7.93 (1H, broad m, NH, exchanges with deuterium oxide), 7.28-6.88 (3H, m, C_3'-H, C_5'-H, C_6-H), 6.49 [1H, d($J_{3,4}$ = 10), C_4-H], 5.13 [1H, d($J_{3,4}$ = 10)

of d($J_{2,3}$ = 3.5), C_3-H], 4.27 (1H, m, C_2-H), 1.7-0.65 (9H, m, n-Bu). The multiplet due to the C_3-H signal sharpens considerably after D_2O exchange. Mass calculated for $C_{15}H_{18}N_2O$, 242.1415; found, 242.1417. Extraction of the silica gel fraction (Rf 0.67) gave 2-n-butyl-5-(4'-pyridylcarbonyl)-pyridine (LXXXVd) as a light yellow oil (0.064 g, 8.6%). ν_{max} (film) (cm^{-1}): 1670 (C=O); nmr δ: 8.95-8.72 (3H, m, $C_{2'}$-H, $C_{6'}$-H, C_6-H), 8.04 [1H, d($J_{3,4}$ = 8) of d($J_{4,6}$ = 2.5), C_4-H], 7.65-7.48 (2H, m, $C_{3'}$-H, $C_{5'}$-H), 7.29 [1H, d($J_{3,4}$ = 8), C_3-H), 2.9 [2H, t($J_{CH_2-CH_2}$ = 7), $C\underline{H_2}C_3H_7$], 2.07-0.72 (7H, m, $CH_2C_3\underline{H_7}$]; mass calculated for $C_{15}H_{16}N_2O$, 240.1259; found, 240.1256. Extraction of the silica gel fraction (Rf 0.94) gave 2-n-butylpyridine (CXXId) as a light yellow oil (0.02 g, 4.8%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (Rf 0.85) gave 4-methoxycarbonylpyridine (CXVIIId) as a colorless oil (0.07 g, 16.4%) identical (nmr) with an authentic sample.

5.3.4.0.0 Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with 2-ethoxycarbonylpyridine

In a dry nitrogen atmosphere 2-ethoxycarbonylpyridine (CXVIIIe) (1.53 g, 10.1 mmol) in anhydrous ether (5 ml) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (LXXXIb) (1.45 g, 10.1 mmol, prepared according to the procedure outlined in section 5.3.0.0.0) in anhydrous ether (60 ml) at room temperature. The resulting rusty-brown suspension was stirred for a further 1 hr and water (100 ml) was added. Extraction with chloroform (5x50 ml), drying (Na_2SO_4) and evaporation of the solvent

in vacuo gave a red oil (3.025 g) of which 0.5 g was subjected to preparative thin-layer chromatography on eight silica gel plates using ether-methanol (15:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 1) gave 2-n-butylpyridine (CXXIe) as a dark yellow oil (0.034 g, 15.1%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (R_f 0.95) gave 2-ethoxycarbonylpyridine (CXVIIIe) as a light yellow oil (0.039 g, 15.5%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (R_f 0.54) gave 2-n-butyl-5-(2'-pyridylcarbonyl)-1,2-dihydropyridine (CXXe) as a bright yellow oil (0.192 g, 47.5%). ν_{max} (film) (cm^{-1}): 3250 (NH), 1648 (C=O), 1570 (C=C); nmr δ: 8.52 (1H, m, C_6'-H), 8.25-7.03 (5H, m, C_6-H, C_3'-H, C_4'-H, C_5'-H, NH, exchanges with deuterium oxide), 6.70 [1H, d($J_{3,4}$ = 10), C_4-H], 5.14 [1H, d($J_{3,4}$ = 10), C_3-H], 4.30 (1H, m, C_2-H), 1.95-0.7 (9H, m, n-Bu). After D_2O exchange the C_4-H multiplet appears as a doublet ($J_{3,4}$ = 10) of doublets ($J_{2,4}$ = 1.5) of doublets ($J_{4,6}$ = 1.5). The C_3-H multiplet appears as a doublet ($J_{3,4}$ = 10) of doublets ($J_{2,3}$ = 3.5); mass calculated for $C_{15}H_{18}N_2O$, 242.1415; found, 242.1412. Extraction of the silica gel fraction (R_f 0.81) gave 2-n-butyl-5-(2'-pyridylcarbonyl)-pyridine (LXXXVe) as a colorless oil (0.016 g, 4.0%). ν_{max} (film) (cm^{-1}): 1670 (C=O); nmr δ: 9.36 [1H, d($J_{4,6}$ = 2.5), C_6-H], 8.75 [1H, d($J_{5',6'}$ = 5) of d($J_{4',6'}$ = 2) of d($J_{3',6'}$ = 1), $C_{6'}$-H], 8.4 [1H, d($J_{3,4}$ = 8) of d($J_{4,6}$ = 2.5), C_4-H], 8.22-7.46 (3H, m, $C_{4'}$-H, $C_{3'}$-H, $C_{5'}$-H), 7.3 [1H, d($J_{3,4}$ = 8), C_3-H], 2.88 [2H, t($J_{CH_2-CH_2}$ = 7), $\underline{H_2}$: $CH_2C_3H_7$], 2.24-0.68 (7H, m, $CH_2C_3H_7$); mass calculated for $C_{15}H_{16}N_2O$, 240.1259; found, 240.1247.

5.3.5.0.0 Reaction of N-lithio-2-methyl-1,2-dihydropyridine with methyl chloroformate

In a dry nitrogen atmosphere methyl chloroformate (2.49 g, 26.3 mmol) in anhydrous ether (10 ml) was added dropwise with stirring to a solution of N-lithio-2-methyl-1,2-dihydropyridine (LXXXIa) (3.76 g, 26.3 mmol prepared according to the procedure outlined in section 5.3.0.0.0) in anhydrous ether (60 ml) at -77°. The resulting clear yellow solution was allowed to warm to room temperature over a 2 hr period and water (100 ml) was added. Extraction with ether (6x50 ml), drying (Na_2SO_4) and evaporation of the solvent *in vacuo* gave a yellowish-brown oil (3.184 g). Vpc analysis on a 5 ft x 1/4 in column packed with 3% OV-101 on Chrom W (80-100 mesh) with a He flow rate of 55 ml/min and a column temperature of 130° gave 2-methylpyridine (CXXIa) identical (ir) with an authentic sample (7.3%, retention time 0.98 min). A column temperature of 180° gave N-methoxycarbonyl-2-methyl-1,2-dihydropyridine (LXXXIVa) (7%, retention time 2 min). ν_{max} (film) (cm^{-1}): 1718 (C=O); nmr δ: 6.65 [1H, d($J_{5,6}$ = 7.5), C_6-H], 5.91 [1H, d($J_{3,4}$ = 8.75) of d($J_{4,5}$ = 5.5), C_4-H], 5.63 [1H, d($J_{2,3}$ = 5), C_3-H], 5.3 (1H, m, C_5-H), 4.86 (1H, m, C_2-H), 3.78 (3H, s, OMe), 1.14 [3H, d(J = 6.5), CH_3]; mass calculated for $C_8H_{11}NO_2$, 153.0789; found, 153.0787. A column temperature of 180° also gave 1,5-dimethoxycarbonyl-2-methyl-1,2-dihydropyridine (CXIXa) (10%, retention time 6 min). ν_{max} (film) (cm^{-1}): 1734, 1712 (C=O); mass calculated for $C_{10}H_{13}NO_4$, 211.0845; found, 211.0837.

5.4.0.0.0 Catalytic Hydrogenation of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine

N-Methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) (0.37 g, 1.72 mmol, prepared from methyl chloroformate using the procedure outlined in section 5.2.0.0.0) was subjected to reduction using hydrogen gas (30 psi) and 10% palladium-charcoal (0.093 g) in methanol (100 ml) for 6 hr. Filtration and evaporation of the solvent in vacuo gave a yellow oil (0.354 g) of which 0.3 g was subjected to preparative thin-layer chromatography on four silica gel plates using ether-benzene (1:1 v/v) as the development solvent. Extraction of the silica gel fraction (Rf 0.87) gave N-methoxycarbonyl-2-phenylpiperidine (CXXV) as a yellow oil (0.267 g, 83%). ν_{max} (film) (cm^{-1}): 1700 (C=O); nmr δ: 7.42-6.95 (5H, m, Ph), 5.45 (1H, m, C_2-H), 3.69 (3H, s, OMe), 3.32-1.16 (8H, m, $(CH_2)_4$); mass calculated for $C_{13}H_{17}NO_2$, 219.1259; found, 219.1263.

5.5.0.0.0 Catalytic Hydrogenation of 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine

1,5-Dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (CXIXb) (0.7 g, 2.77 mmol) was subjected to reduction using hydrogen gas (40 psi) and 10% palladium-charcoal (0.35 g) in methanol (100 ml) and chloroform (40 ml) for 3 hr. Filtration and evaporation of the solvent in vacuo gave a bright yellow oil (0.62 g) of which 0.3 g was subjected to preparative thin-layer chromatography on five silica gel plates (1 mm) using benzene-chloroform-acetone (10:1:1 v/v) as the development solvent. Extraction of the silica gel

fraction (R_f 0.88) gave 1,5-dimethoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridine (CXXVI) as a pale yellow oil (0.171 g, 50.3%). ν_{max} (film) (cm^{-1}): 1730, 1708 (C=O), 1640 (C=C); nmr δ: 7.97 (1H, s, C_6-H), 4.23 (1H, m, C_2-H), 3.8 (3H, s, OMe), 3.7 (3H, s, OMe), 2.45-1.6 [4H, m, $(CH_2)_2$], 1.6-0.67 (9H, m, n-Bu); mass calculated for $C_{13}H_{21}NO_4$, 255.1465; found, 255.1471.

5.6.0.0.0 Reaction of N-acetyl-2-phenyl-1,2-dihydropyridine carbanion with iodomethane

In a dry nitrogen atmosphere N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa)[189] (0.44 g, 2.2 mmol) in anhydrous tetrahydrofuran (2.5 ml) was added dropwise with stirring to a solution of lithium diisopropylamide[241] (0.235 g, 2.2 mmol) in anhydrous tetrahydrofuran (10 ml) at -77°. To the resulting deep red solution was added iodomethane (0.314 g, 2.2 mmol) in anhydrous tetrahydrofuran (1 ml) dropwise at -77°. The resulting yellow solution was allowed to warm to room temperature over a 1 hr period and a saturated solution of ammonium chloride (20 ml) was added. Extraction with ether (3x20 ml), drying (Na_2SO_4) and evaporation of the solvent in vacuo gave a dark yellow oil (0.365 g) of which 0.2 g was subjected to preparative thin-layer chromatography on four silica gel plates using benzene-ether (1:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.97) gave N-propionyl-2-phenyl-1,2-dihydropyridine (CXXXI, R^1 = Me) as a yellow oil (0.14 g, 54.3%). ν_{max} (film) (cm^{-1}): 1678 (C=O), 1650, 1583 (C=C); nmr δ: 7.28 (5H, m, Ph), 6.49 [1H, d($J_{5,6}$ = 7.5), C_6-H], 6.18 [1H, d($J_{2,3}$ = 5.5), C_2-H],

5.95 (1H, m, C_4-H), 5.75 (1H, m, C_3-H), 5.3 (1H, m, C_5-H), 2.36 [2H, q($J_{CH_2-CH_3}$ = 7), $C\underline{H_2}CH_3$], 1.1 [3H, t($J_{CH_2-CH_3}$ = 7), $CH_2C\underline{H_3}$]; mass calculated for $C_{14}H_{15}NO$, 213.1154; found, 213.1152. Extraction of the silica gel fraction (R_f 0.83) gave N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa) as a light yellow oil (0.015 g, 6.2%) identical (R_f, ir) with an authentic sample.

5.7.0.0.0 Diels-Alder cycloaddition products from reaction of 1,2-dihydropyridines with 1,2,4-triazoline-3,5-diones

General Procedure: In a dry nitrogen atmosphere the appropriate dihydropyridine (1 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of the 1,2,4-triazoline-3,5-dione (1 mmol) in anhydrous dichloromethane (10-100 ml). Once the addition was complete the deep red color of the triazoline dione was discharged to a nearly colorless solution. Evaporation of the solvent *in vacuo* gave the Diels-Alder cycloaddition product generally in quantitative yield.

5.7.1.0.0 Reaction of N-acetyl-2-phenyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa)[189] (0.113 g, 0.57 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (0.1 g, 0.57 mmol) in anhydrous dichloromethane (10 ml) at -77°. The

resulting clear solution was allowed to warm to room temperature and the solvent evaporated in vacuo to give a mixture of the stereoisomers 5-endo-acetyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXXXIXa, 68%) and 5-exo-acetyl-6-endo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXLa, 32%) as an off white solid (0.213 g, 100%), mp 181-183°; ν_{max} (cm^{-1}): 1784, 1715 (sh), 1709 (C=O), 1665 (C=C); nmr δ: 7.58-7.05 (11H, m, Ph, C_4-H), 6.82 [1H, d($J_{7,8}$ = 8) of d ($J_{4,8}$ = 5.5) of d($J_{1,8}$ = 1.75), C_8-H], 6.5-6.05 (1H, m, C_7-H), 5.42, 5.16 (1H, m, exo-C_6-H, endo-C_6-H), 5.08 (1H, m, C_1-H), 2.34, 1.79 (3H, s, exo-CH_3, endo-CH_3); mass calculated for $C_{21}H_{18}N_4O_3$, 374.1379; found, 374.1377.

5.7.2.0.0 Reaction of N-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-ethoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXc)[189] (0.247 g, 1.08 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (0.189 g, 1.08 mmol) in anhydrous dichloromethane (10 ml) at -77°. The resulting clear solution was allowed to warm to room temperature and the solvent evaporated in vacuo to give 5-endo-ethoxycarbonyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2] oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXXXIXd) as an off-white solid (0.436 g, 100%), mp 150-154°; ν_{max} (cm^{-1}): 1790, 1718 (C=O); nmr δ: 7.6-7 (10H, m, Ph), 6.74 (2H, m, C_4-H, C_8-H), 6.12 [1H, d($J_{7,8}$ = 9.5) of d($J_{1,7}$ = 5),

C_7-H], 5.21 [1H, d($J_{1,6}$ = 2.5), C_6-H], 5.11 [1H, d($J_{1,7}$ = 5) of d($J_{1,6}$ = 2.5), C_1-H], 4.08 [2H, q($J_{CH_2\text{-}CH_3}$ = 7), OCH_2], 1.1 [3H, t, ($J_{CH_2\text{-}CH_3}$ = 7), CH_3]; mass calculated for $C_{22}H_{20}N_4O_4$, 404.1478; found, 404.1485.

5.7.3.0.0 Reaction of N-benzoyl-2-phenyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-benzoyl-2-phenyl-1,2-dihydropyridine (XXXIXd)[189] (0.5 g, 1.93 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (0.338 g, 1.93 mmol) in anhydrous dichloromethane (40 ml) at room temperature. The resulting clear solution was stirred for a further 0.5 hr. Evaporation of the solvent *in vacuo* gave 5-*endo*-benzoyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide (CXXXIXe) as an off-white solid (0.841 g, 100%), mp 202°-204° (from DMSO); ν_{max} (cm^{-1}): 1790, 1720, 1700 (sh), (C=O); nmr (DMSO-d_6) δ: 7.59, 7.46, 7.33 (15H, m, Ph), 7.33-6.94 (1H, m, C_4-H), 6.63-6.27 (2H, m, C_7-H, C_8-H), 5.62 [1H, d($J_{1,6}$ = 2.5), C_6-H], 5.35 (1H, m, C_1-H); mass calculated for $C_{26}H_{20}N_4O_3$, 436.1535; found, 436.1531.

5.7.4.0.0 Reaction of N-methoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-methoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (LXXXIVb) (0.39 g, 2 mmol) in anhydrous dichloromethane

(10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (0.35 g, 2 mmol) in anhydrous dichloromethane (10 ml) at room temperature. The resulting clear solution was stirred for a further 0.5 hr. Evaporation of the solvent *in vacuo* gave 5-*endo*-methoxycarbonyl-6-*exo*-*n*-butyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide (CXXXIXf) as a light yellow semi-solid (0.74 g, 100%) mp 35-38°; ν_{max} (film) (cm^{-1}): 1782, 1726, 1712 (sh) (C=O); nmr δ: 7.52-7.23 (6H, m, Ph, C_4-H), 6.67-6.28 (2H, m, C_7-H, C_8-H), 5.06 (1H, m, C_1-H), 4.2-3.79 (1H, m, C_6-H), 3.79 (3H, s, OMe), 1.53-0.7 (9H, m, *n*-Bu); mass calculated for $C_{19}H_{22}N_4O_4$, 370.1641; found, 370.1654.

5.7.5.0.0 Reaction of 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere 1,5-dimethoxycarbonyl-2-*n*-butyl-1,2-dihydropyridine (CXIXb) (0.4 g, 1.58 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (0.277 g, 1.58 mmol) in anhydrous dichloromethane (20 ml) at room temperature. The resulting clear solution was stirred for a further 0.5 hr. Evaporation of the solvent *in vacuo* gave 5-*endo*-8-dimethoxycarbonyl-6-*exo*-*n*-butyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide (CXXXIXg) as a light yellow semi-solid (0.676 g, 100%), mp 55-60°; ν_{max} (cm^{-1}): 1780, 1728, 1715 (sh) (C=O); nmr δ: 7.5-7.23 (6H, m, Ph, C_4-H), 6.95 (1H, m, C_7-H), 5.21 [1H, d($J_{1,7}$ = 5) of d($J_{1,6}$ = 2.5), C_1-H], 4.25-3.84 (1H, m,

C_6-H), 3.84 (3H, s, OMe), 3.81 (3H, s, OMe), 1.62-0.77 (9H, m, _n_-Bu); mass calculated for $C_{21}H_{24}N_4O_6$, 428.1696; found, 428.1680.

5.7.6.0.0 Reaction of N-methoxycarbonyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-methoxycarbonyl-1,2-dihydropyridine (LV)[144] (1.19 g, 8.57 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (1.5 g, 8.57 mmol) in anhydrous dichloromethane (10 ml) at room temperature. The resulting clear solution was stirred for a further 4.5 hr. Evaporation of the solvent _in vacuo_ gave _5-endo-methoxycarbonyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide_ (CXXXIXh) as an off-white solid (2.69 g, 100%), mp 152-156° (decomp.); ν_{max} (cm^{-1}): 1779, 1725, 1710 (sh) (C=O); nmr δ: 7.36 (5H, m, Ph), 6.76-6.36 (3H, m, C_4-H, C_7-H, C_8-H), 5.04 [1H, d($J_{1,7}$ = 5) of d($J_{1,6}$ = 2.75), C_1-H], 3.8 [1H, d($J_{6,6'gem}$ = 11) of d($J_{1,6}$ = 2.75), C_6-H or $C_{6'}$-H], 3.73 (3H, s, OMe), 3.17 [1H, d($J_{6,6'gem}$ = 11) of d($J_{1,6}$ = 2.75), C_6-H or $C_{6'}$-H]; mass calculated for $C_{15}H_{14}N_4O_4$, 314.1015; found, 314.1020.

5.7.7.0.0 Reaction of N-methanesulfonyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-methanesulfonyl-1,2-dihydropyridine (CXXXVII)[243] (1.36 g, 8.57 mmol) in anhydrous dichloromethane

(10 ml) was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (CXXXVIIIa)[238,239] (1.5 g, 8.57 mmol) in anhydrous dichloromethane (40 ml) at room temperature. The resulting clear solution was stirred for a further 0.5 hr. Evaporation of the solvent in vacuo gave 5-endo-methanesulfonyl-2,3,5-triazabicyclo-[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (CXXXIXj) as an off-white solid (2.862 g, 100%), mp 170-175° (from acetone); ν_{max} (cm^{-1}): 1794, 1725 (C=O); nmr (DMSO-d_6) δ: 7.45 (5H, m, Ph), 6.96-6.6 (2H, m, C_7-H, C_8-H), 6.06 [1H, d($J_{4,8}$ = 6) of d($J_{4,7}$ = 1.5), C_4-H], 5.2 (1H, m, C_1-H), 3.81 [1H, d($J_{6,6'gem}$ = 10.5) of d($J_{1,6}$ = 3), C_6-H or $C_{6'}$-H], 3.24 [1H, d($J_{6,6'gem}$ = 10.5) of d($J_{1,6}$ = 3), C_6-H or $C_{6'}$-H], 3.08 (3H, s, SO_2Me); mass calculated for $C_{14}H_{14}N_4O_4{}^{32}S$, 334.0736; found, 334.0752.

5.7.8.0.0 Reaction of N-acetyl-2-phenyl-1,2-dihydropyridine with 4-ethyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa)[190] (1.45 g, 7.28 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-ethyl-1,2,4-triazoline-3,5-dione (CXXXVIIIb)[238,239] (0.924 g, 7.28 mmol) in anhydrous dichloromethane (10 ml) at room temperature. The resulting clear solution was stirred for a further 0.5 hr. Evaporation of the solvent in vacuo gave a mixture of the stereoisomers 5-endo-acetyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-ethylimide (CXXXIXb, 69%) and 5-exo-acetyl-6-endo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic

acid N-ethylimide (CXLb, 31%) as a yellow solid (2.373 g, 100%), mp 70°; ν_{max} (cm^{-1}): 1782, 1720 (C=O); nmr δ: 7.5-6.91 (6H, m, Ph, C_4-H), 6.68 (1H, m, C_8-H), 6.08 (1H, m, C_7-H), 5.39-4.82 (2H, m, C_1-H, exo-C_6-H, endo-C_6-H), 3.47 [2H, q[$J_{CH_2-CH_3}$ = 7], $C\underline{H_2}CH_3$], 2.3, 1.78 (3H, s, exo-CH_3, endo-CH_3), 1.17 [3H, t($J_{CH_2-CH_3}$ = 7), $CH_2C\underline{H_3}$]; mass calculated for $C_{17}H_{18}N_4O_3$, 326.1379; found, 326.1374.

5.7.9.0.0 Reaction of N-methoxycarbonyl-1,2-dihydropyridine with 4-ethyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-methoxycarbonyl-1,2-dihydropyridine (LV)[144] (0.821 g, 5.91 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-ethyl-1,2,4-triazoline-3,5-dione (CXXXVIIIb)[238,239] (0.75 g, 5.91 mmol) in anhydrous dichloromethane (10 ml) at -77°. The resulting clear solution was allowed to warm to room temperature and the solvent was evaporated *in vacuo* to give 5-*endo*-methoxycarbonyl-2,3,5-triazabicyclo[2.2.2]-oct-7-ene-2,3-*endo*-dicarboxylic acid N-ethylimide (CXXXIXi) as a yellow semi-solid (1.413 g, 92%). ν_{max} (cm^{-1}): 1756, 1708 (C=O); nmr δ: 6.3-5.75 (2H, m, C_8-H, C_7-H or C_4-H), 5.67-5.33 (1H, m, C_4-H or C_7-H), 4.56-4.19 (1H, m, C_1-H), 4.19-3.33 (7H, m, OMe, CH_2, C_6-H, C_6'-H), 1.24 [3H, t($J_{CH_2-CH_3}$ = 7), $CH_2C\underline{H_3}$]; mass calculated for $C_{11}H_{14}N_4O_4$, 266.1015; found, 266.1016.

5.7.10.0.0 Reaction of N-methanesulfonyl-1,2-dihydropyridine with 4-ethyl-1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-methanesulfonyl-1,2-dihydropyridine (CXXXVII)[243] (0.45 g, 2.8 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4-ethyl-1,2,4-triazoline-3,5-dione (CXXXVIIIb)[238,239] (0.359 g, 2.8 mmol) in anhydrous dichloromethane (10 ml) at room temperature. The resulting clear solution was stirred for a further 0.5 hr. Evaporation of the solvent *in vacuo* gave *5-endo-methanesulfonyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-ethylimide* (CXXXIXk) as a yellow semi-solid (0.713 g, 89%). ν_{max} (cm^{-1}): 1768, 1702 (C=O); nmr δ: 6.52-5.71 (3H, m, C_4-H, C_7-H, C_8-H), 5.25 (1H, m, C_1-H), 4.18-3.24 (3H, m, C_6-H, C_6'-H, CH_2), 3.02 (3H, s, SO_2Me), 1.25[3H, t($J_{CH_2-CH_3}$ = 7), $CH_2\underline{CH_3}$]; mass calculated for $C_{10}H_{14}N_4O_4{}^{32}S$, 286.0736; found, 286.0740.

5.7.11.0.0 Reaction of N-acetyl-2-phenyl-1,2-dihydropyridine with 1,2,4-triazoline-3,5-dione

In a dry nitrogen atmosphere N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa)[190] (0.153 g, 0.77 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 1,2,4-triazoline-3,5-dione (CXXXVIIIc)[238] (0.076 g, 0.77 mmol) in anhydrous dichloromethane (100 ml) at 0°. The reaction was allowed to warm to room temperature during which time the red color of the triazoline dione was discharged. Evaporation of the solvent *in vacuo* gave a

mixture of stereoisomers 5-endo-acetyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid imide (CXXXIXc, 43%) and 5-exo-acetyl-6-endo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid imide (CXLc, 26%) as a light yellow solid (0.158 g, 69%), mp 217-219° (chloroform washed); ν_{max} (cm^{-1}): 1778, 1720 (C=O); nmr (DMSO-d_6) δ: 7.56-7.04 (5H, m, Ph), 7-6.63 (2H, m, C_4-H, C_8-H), 6.59-6 (2H, m, C_7-H, NH, exchanges with deuterium oxide), 5.73, 5.42 (1H, m, exo-C_6-H, endo-C_6-H), 5.16 (1H, m, C_1-H), 2.3, 1.72 (3H, s, exo-CH_3, endo-CH_3); mass calculated for $C_{15}H_{14}N_4O_3$, 298.1066; found, 298.1059.

5.8.0.0.0 Reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine with 4,4-diethyl-1,2-pyrazoline-3,5-dione

In a dry nitrogen atmosphere N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) (0.412 g, 1.92 mmol, prepared with methyl chloroformate using the procedure outlined in section 5.2.0.0.0) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of 4,4-diethyl-1,2-pyrazoline-3,5-dione (CLIV)[240] (0.295 g, 1.92 mmol) in anhydrous dichloromethane (100 ml) at 0°. The reaction was allowed to warm to room temperature during which time the blue color of the pyrazoline dione was discharged. Evaporation of the solvent *in vacuo* gave 5-endo-methoxycarbonyl-6-exo-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-diethylmalonimide (CLV) as a yellow semi-solid (0.708 g, 100%). ν_{max} (cm^{-1}): 1745, 1712, 1700 (sh) (C=O); nmr δ: 7.47-7.05 (6H, m, Ph, C_4-H), 6.78 (1H, m, C_8-H), 6.12 (1H, m, C_7-H), 5.35-5.06 (2H, m, C_1-H, C_6-H), 3.61 (3H,

s, OMe), 1.8 [2H, q($J_{CH_2-CH_3}$ = 7), *anti*-CH_2CH$_3$], 1.75 [2H, q($J_{CH_2-CH_3}$ = 7), *syn*-CH_2CH$_3$], 0.95 [3H, t($J_{CH_2-CH_3}$ = 7), *anti*-CH$_2$CH_3], 0.79 [3H, t($J_{CH_2-CH_3}$ = 7), *syn*-CH$_2$CH_3]; mass calculated for $C_{20}H_{23}N_3O_4$, 369.1683; found, 369.1686.

5.9.0.0.0 Diels-Alder Cycloaddition Products from reaction of 1,2-dihydropyridines with maleimides

5.9.1.0.0 Reaction of N-acetyl-2-phenyl-1,2-dihydropyridine with N-phenylmaleimide

In a dry atmosphere N-acetyl-2-phenyl-1,2-dihydropyridine (XXXIXa)^{190} (1.37 g, 6.88 mmol) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of N-phenylmaleimide (CLVIa) (1.19 g, 6.88 mmol) in anhydrous dichloromethane (50 ml) at reflux temperature. The reaction mixture was boiled under reflux for 5 days after which evaporation of the solvent *in vacuo* gave a mixture of stereoisomers *5-endo-acetyl-6-exo-phenyl-5-azabicyclo-[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide* (CLVIIa, 75%) and *5-exo-acetyl-6-endo-phenyl-5-azabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide* (CLVIIIa, 25%) as an off white solid (2.559 g, 100%), mp 269-271° (acetone washed); ν_{max} (cm^{-1}): 1775, 1710 (C=O), 1650 (C=C); nmr δ: 7.5-7.02 (10H, m, Ph), 6.61 [1H, d($J_{7,8}$ = 8) of d($J_{4,8}$ = 6) of d($J_{1,8}$ = 1.25), C_8-H], 6.14-5.93 (2H, m, C_4-H, C_7-H), 5.09, 4.8 (1H, m, *exo*-C_6-H, *endo*-C_6-H), 3.64 (1H, m, C_1-H), 3.52 [1H, d($J_{2,3}$ = 8) of d($J_{3,4}$ = 4), C_3-H], 3.34 [1H, d($J_{2,3}$ = 8) of d($J_{1,2}$ = 3), C_2-H], 2.3, 1.77 (3H,

s, exo-CH_3, endo-CH_3); mass calculated for $C_{23}H_{20}N_2O_3$, 372.1474; found, 372.1465.

5.9.2.0.0 Reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine with N-methylmaleimide

In a dry argon atmosphere N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) (0.4 g, 1.86 mmol, prepared with methyl chloroformate using the procedure outlined in section 5.2.0.0.0) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of N-methylmaleimide (CLVIb) (0.207 g, 1.86 mmol) and aluminum chloride (1.24 g, 9.3 mmol) in anhydrous dichloromethane (50 ml) at reflux temperature. Refluxing for 1 hr, washing with water (100 ml), 5% sodium bicarbonate (2x100 ml), water (100 ml), drying (Na_2SO_4), and solvent evaporation in vacuo gave a low melting off-white solid which was chromatographed on a 2.5 x 35 cm silica column. Elution with benzene-ether (750 ml) (1:2 v/v) gave 5-endo-methoxycarbonyl-6-exo-phenyl-5-azabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-methylimide (CLVIIb, 0.339 g, 56%). ν_{max} (cm^{-1}): 1772 (broad) (C=O); nmr δ: 7.38-6.84 (5H, m, Ph), 6.37 (1H, m, C_8-H), 5.78 (1H, m, C_7-H), 5.32 (1H, m, C_4-H), 4.75 (1H, m, C_6-H), 3.8-3.1 (6H, m, C_1-H, C_2-H, C_3-H, OMe), 2.8 (3H, s, NMe); mass calculated for $C_{18}H_{18}N_2O_4$, 326.1267; found, 326.1251.

5.9.3.0.0 Reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine with maleimide

In a dry argon atmosphere N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (XXXIXb) (0.44 g, 2.5 mmol, prepared with methyl chloroformate using the procedure outlined in section 5.2.0.0.0) in anhydrous dichloromethane (10 ml) was added dropwise with stirring to a solution of maleimide (CLVIc) (0.198 g, 2.5 mmol) and aluminum chloride (1.364 g, 10.2 mmol) in anhydrous dichloromethane (100 ml) at reflux temperature. Refluxing for 1.5 hr, washing with water (100 ml), 5% sodium bicarbonate (2x100 ml), water (100 ml), drying (Na_2SO_4) and solvent evaporation *in vacuo* gave a yellow semi-solid which precipitated from benzene-cyclohexane-methanol (10:35:1) (10 ml) giving 5-*endo*-methoxycarbonyl-6-*exo*-phenyl-5-azabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid imide (CLVIIc, 0.333 g, 52%). ν_{max} (cm^{-1}): 1765 (broad) (C=O); nmr δ: 8.64 (1H, s, NH, exchanges with deuterium oxide), 7.48-7 (5H, m, Ph), 6.53 (1H, m, C_8-H), 5.95 (1H, m, C_7-H), 5.39 (1H, m, C_4-H), 4.75 (1H, m, C_6-H), 3.82-3.34 (5H, m, C_1-H, C_3-H, OMe), 3.25 (1H, m, C_2-H); mass calculated for $C_{17}H_{16}N_2O_4$, 312.1110; found, 312.1118.

5.10.0.0.0 Catalytic Hydrogenation of Selected Diels-Alder Adducts

5.10.1.0.0 Catalytic hydrogenation of 5-*endo*-ethoxycarbonyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide

5-*Endo*-ethoxycarbonyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-dicarboxylic acid N-phenylimide (CXXXIXd) (0.25 g, 0.62 mmol)

was subjected to reduction using hydrogen gas (27 psi) and 10% palladium-charcoal (0.1 g) in methanol (75 ml) for 4.5 hr. Filtration and evaporation of the solvent *in vacuo* gave a dark yellow oil (0.273 g) of which 0.09 g was subjected to preparative thin-layer chromatography on one silica gel plate using benzene-ether (5:2 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.55) gave 5-*endo*-ethoxycarbonyl-6-*exo*-phenyl-2,3,5-triazabicyclo-[2.2.2]octane-2,3-endo-dicarboxylic acid N-phenylimide (CXLId) as a colorless oil (0.05 g, 60.6%). nmr δ: 7.6-7 (10H, m, Ph), 6.43 (1H, m, C_4-H), 5.27 (1H, m, C_6-H), 4.55 (1H, m, C_1-H), 4.15 [2H, q($J_{CH_2-CH_3}$ = 7), OCH_2], 2.52-1.43 (4H, m, C_7-H, C_8-H), 1.17 [3H, t($J_{CH_2-CH_3}$ = 7), CH_3]; mass calculated for $C_{22}H_{22}N_4O_4$, 406.1641; found, 406.1629.

5.10.2.0.0 Catalytic hydrogenation of a mixture of the stereoisomers 5-*endo*-acetyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]-oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide and 5-*exo*-acetyl-6-*endo*-phenyl-2,3,5-triazabicyclo[2.2.2]-oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenylimide

The titled mixture (CXXXIXa, CXLa) (0.2 g, 0.535 mmol) was subjected to reduction using hydrogen gas (30 psi) and 10% palladium-charcoal (0.05 g) in methanol (100 ml) for 2.5 hr. Filtration and evaporation of the solvent *in vacuo* gave a dark yellow oil (0.3 g) which was subjected to preparative thin layer chromatography on five silica gel plates using benzene-ether (5:2 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.29) gave

a mixture of stereoisomers 5-*endo*-acetyl-6-*exo*-phenyl-2,3,5-triazabicyclo[2.2.2]octane-2,3-*endo*-dicarboxylic acid N-phenylimide (CXLIa) and 5-*exo*-acetyl-6-*endo*-phenyl-2,3,5-triazabicyclo[2.2.2]octane-2,3-*endo*-dicarboxylic acid N-phenylimide (CXLIIa) as a colorless oil (0.171 g, 85.1%). nmr δ: 7.77-7.09 (10H, m, Ph), 6.18 (1H, m, C_4-H), 5.4 (1H, m, C_6-H), 4.62 (1H, m, C_1-H), 2.64-1.56 (4H, m, C_7-H, C_8-H), 2.36 (3H, s, CH_3); mass calculated for $C_{21}H_{20}N_4O_3$, 376.1535; found, 376.1529.

5.11.0.0.0 Preparation of 10-methyl- and 10-(dimethylaminoalkyl)-10H-pyrido[3,2-b][1,4]benzothiazines

5.11.1.0.0 Alkylation of 10H-pyrido[3,2-b][1,4]benzothiazine with Iodomethane

In a dry nitrogen atmosphere 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) (2 g, 10 mmol) was added portion-wise with stirring to a suspension of sodium hydride (0.528 g, 22 mmol) in anhydrous tetrahydrofuran (100 ml) at room temperature. The rate of addition was such that a controlled evolution of hydrogen gas was achieved. The resulting dark yellowish-brown suspension was stirred at room temperature for 1 hr and iodomethane (3.12 g, 22 mmol) was added dropwise. Stirring at room temperature for a further 1 hr gave a yellowish suspension which was filtered under a nitrogen stream. The filtrate was treated with water (80 ml), extracted with ether (4x50 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a dark yellow solid (1.902 g, 89%). Recrystallization from hexanes

(bp 68.4-68.9°) gave 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) as a yellow solid, mp 84° (reported[244], mp 86°); nmr δ: 8.08 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 1.75), C_2-H], 7.29 [1H, d($J_{3,4}$ = 8) of d($J_{2,4}$ = 1.75), C_4-H], 7.29-6.6 (5H, m, Ph, C_3-H), 3.44 (3H, s, NMe); mass calculated for $C_{12}H_{10}N_2{}^{32}S$, 214.0563; found, 214.0561.

5.11.2.0.0 Alkylation of 10H-pyrido[3,2-b][1,4]benzothiazine with 2-dimethylaminoethyl chloride hydrochloride

In a dry nitrogen atmosphere 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) (2 g, 10 mmol) was added portionwise with stirring to a suspension of sodium hydride (0.792 g, 33 mmol) in anhydrous toluene (125 ml). The resulting dark yellow suspension was boiled under reflux for 1 hr, cooled, and 2-dimethylaminoethyl chloride hydrochloride (1.584 g, 11 mmol) was added portionwise. The mixture was allowed to boil under reflux for 24 hr to give a dark gold-brown suspension which was cooled to room temperature, filtered under a nitrogen stream, and the filtrate treated with water (100 ml). The organic layer was separated and the solvent removed *in vacuo* to give a dark brown oil (3.142 g) which was chromatographed on a 2.5 x 6 cm silica gel column. Elution with benzene (850 ml) gave 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) as a yellow solid (0.249 g, 12.5%) identical (nmr, mp) with an authentic sample. Further elution with ether (500 ml) gave 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIc) as a light yellow oil[244] (1.623 g, 59.9%). nmr δ: 8 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 1.75), C_2-H], 7.38-6.59 (6H, m, Ph, C_3-H, C_4-H), 4.28 [2H, t($J_{CH_2\text{-}CH_2}$ = 7),

$C\underline{H_2}CH_2N(Me)_2$], 2.75 [2H, t($J_{CH_2-CH_2}$ = 7), $CH_2C\underline{H_2}N(Me)_2$], 2.39 [6H, s, $N(Me)_2$]; mass calculated for $C_{15}H_{17}N_3{}^{32}S$, 271.1140; found, 271.1146.

5.11.3.0.0 Alkylation of 10H-pyrido[3,2-b][1,4]benzothiazine with 2-dimethylaminoisopropyl chloride hydrochloride

In a dry nitrogen atmosphere 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) (7 g, 35 mmol) was added portionwise with stirring to a suspension of sodium hydride (3.024 g, 126 mmol) in anhydrous toluene (250 ml). The resulting dark yellow suspension was boiled under reflux for 1.5 hr, cooled and 2-dimethylaminoisopropyl chloride hydrochloride (6.636 g, 42 mmol) was added portionwise. The mixture was allowed to boil under reflux for 42 hr to give a dark gold-brown suspension which was cooled to room temperature, filtered under a nitrogen stream, and the filtrate treated with water (100 ml). Extraction with chloroform (3x50 ml), drying (Na_2SO_4), and evaporation of the solvent *in vacuo* gave a dark brown oil which was chromatographed on a 2.5 x 25 cm silica gel column. Elution with benzene (400 ml) gave 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) as a yellow solid (0.828 g, 11.8%) identical (R_f, nmr) with an authentic sample. Further elution with benzene (400 ml) gave 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIf) as a yellow oil[305] (0.964 g, 9.7%). nmr δ: 7.99 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 1.75), C_2-H], 7.35-6.52 (6H, m, Ph, C_3-H, C_4-H), 4.32 [1H, sextet(J_{CH-CH_2} = J_{CH-CH_3} = 6.5), $C\underline{H}(CH_3)CH_2$], 3[2H, d(J_{CH-CH_2} = 6.5), CH_2], 2.28 (6H, s, $N(Me)_2$), 1.7 [3H, d(J_{CH-CH_3} = 6.5), $CHC\underline{H_3}$]; mass calculated for $C_{16}H_{19}N_3{}^{32}S$,

285.1296; found, 285.1299. Further elution with benzene (450 ml) gave 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIe) as a yellow oil[305] (3.34 g, 33.5%). nmr δ: 8.01 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 1.75), C_2-H], 7.35-6.58 (6H, m, Ph, C_3-H, C_4-H), 4.4-4.15 (2H, m, CH_2), 3.08 (1H, m, CH), 2.32 [6H, s, $N(Me)_2$], 1.02 [3H, d(J_{CH-CH_3} = 6.5), $CH\underline{H_3}$]; mass calculated for $C_{16}H_{19}N_3{}^{32}S$, 285.1296; found, 285,1302.

5.11.4.0.0 Preparation of 10-(3-dimethylaminopropyl)-10H-pyrido-[3,2-b][1,4]benzothiazine from 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine hydrochloride monohydrate (Tolnate)

Potassium carbonate (0.68 g, 4.9 mmol) was added portionwise with stirring to a solution of 10-(3-dimethylaminopropyl)-10H-pyrido-[3,2-b][1,4]benzothiazine hydrochloride monohydrate (1 g, 2.95 mmol) in water (10 ml). The mixture was stirred for 1 hr and extraction with dichloromethane (3x10 ml), drying (Na_2SO_4), and evaporation of the solvent *in vacuo* gave 10-(3-dimethylaminopropyl)-10H-pyrido-[3,2-b][1,4]benzothiazine (CLXXIId) as a light yellow oil[244] (0.841 g, 100%). nmr δ: 7.95 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 2), C_2-H], 7.13 [1H, d($J_{3,4}$ = 7.5) of d($J_{2,4}$ = 2), C_4-H], 7.27-6.48 (5H, m, Ph, C_3-H), 4.1 [2H, t($J_{CH_2-CH_2}$ = 7), $\underline{CH_2}(CH_2)_2N(Me)_2$], 2.57-1.68 (4H, m, $CH_2(\underline{CH_2})_2N(Me)_2$], 2.19 [6H, s, $N(Me)_2$]; mass calculated for $C_{16}H_{19}N_3{}^{32}S$, 285.1296; found, 285.1298.

5.12.0.0.0 The Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-butyllithium and subsequent reaction with electrophilic reagents

General Procedure: In a dry nitrogen atmosphere *n*-butyllithium (5 mmol) was added dropwise with stirring to a solution of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) (5 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting gold-brown solution was stirred at 0° for 1 hr, cooled to -77°, and the appropriate electrophile (5-6 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise. The resulting solution was stirred at -77° for 0.75-1.5 hr, allowed to warm to room temperature over a 1-3 hr period and the reaction products isolated as described in individual cases.

5.12.1.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-butyllithium and methyl chloroformate

The general procedure outlined in section 5.12.0.0.0 was followed. *n*-Butyllithium (0.32 g, 5 mmol), 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) (1.07 g, 5 mmol) and methyl chloroformate (0.567 g, 6 mmol) were stirred at -77° for 1 hr and allowed to warm to room temperature over a 3 hr period. The resulting reddish-orange solution was treated with water (100 ml), extracted with dichloromethane (100 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark red oil (1.75 g) of which 1.1 g was subjected to preparative thin-layer chromatography on twelve silica gel plates using benzene-ethyl acetate (20:1 v/v) as the development solvent.

Extraction of the silica gel fraction (R_f 0.85) gave 1-methoxycarbonyl-2-*n*-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIa) as a dark yellow oil (0.827 g, 79.7%). ν_{max} (film) (cm^{-1}): 1725 (C=O), 1632, 1568 (C=C); nmr δ: 7.26-6.66 (4H, m, Ph), 5.92-5.48 (2H, m, C_3-H, C_4-H), 4.8 (1H, m, C_2-H), 3.7 (3H, s, OMe), 3.18 (3H, s, NMe), 1.98-0.68 (9H, m, *n*-Bu); mass calculated for $C_{18}H_{22}N_2O_2{}^{32}S$, 330.1397; found, 330.1400. Extraction of the silica gel fraction (R_f 0.53) gave a red solid (0.169 g, 19.8%). Recrystallization from hexanes (bp 68.4-68.9°) gave 4-methoxycarbonyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXVIIa) as a red solid, mp 118-20° (decomp.). ν_{max} (cm^{-1}): 1711 (C=O); nmr δ: 8.03 [1H, d($J_{2,3}$ = 5), C_2-H], 7.19 [1H, d($J_{2,3}$ = 5), C_3-H], 7.36-6.6 (4H, m, Ph), 3.94 (3H, s, OMe), 3.39 (3H, s, NMe); mass calculated for $C_{14}H_{12}N_2O_2{}^{32}S$, 272.0617; found, 272.0615.

5.12.2.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with *n*-butyllithium and water followed by thermal treatment of the adduct

The general procedure outlined in section 5.12.0.0.0 was followed. *n*-Butyllithium (0.32 g, 5 mmol) and 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) (1.07 g, 5 mmol) were stirred at 0° for 0.5 hr and allowed to warm to room temperature over a 10 min period. The resulting gold-brown solution was treated with water (50 ml), extracted with dichloromethane (3x50 ml), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a yellow oil (1.36 g). A portion (0.4 g) of this oil was heated at 140° for 1 hr and at 170° for

0.5 hr to give a dark brown oil which was subjected to preparative thin-layer chromatography on six silica gel plates using benzene-ethyl acetate (20:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.95) gave 2-*n*-butyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXIII, R = Me, R^2 = *n*-Bu) as a light yellow oil (0.038 g, 9.6%). nmr δ: 7.39-6.5 (6H, m, Ph, C_3-H, C_4-H), 3.44 (3H, s, NMe), 2.64 [2H, t($J_{CH_2-CH_2C_2H_5}$ = 7), $C\underline{H_2}C_3H_7$], 2-0.68 (7H, m, $CH_2C_3\underline{H_7}$); mass calculated for $C_{16}H_{18}N_2{}^{32}S$, 270.1187; found, 280.1190. Extraction of the silica gel fraction (R_f 0.67) gave 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) as a yellow solid (0.079 g, 25.1%) identical (nmr) with an authentic sample.

5.12.3.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with *n*-butyllithium and deuterium oxide

The general procedure outlined in section 5.12.0.0.0 was followed. The reaction of *n*-butyllithium (0.064 g, 1 mmol) and 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) (0.107 g, 0.5 mmol) in anhydrous tetrahydrofuran (10 ml) was stirred at 0° for 1 hr and then allowed to warm to room temperature over a 3 hr period. The resulting brown solution was treated with deuterium oxide (0.04 g, 2 mmol), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a light yellow oil (0.141 g). A portion (0.13 g) of this oil was subjected to preparative thin-layer chromatography on two silica gel plates using benzene-ethyl acetate (10:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.58) gave

4-deutero-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLVIII) as a yellow semi-solid (0.015 g, 13.9%). nmr δ: 8.02 [1H, d($J_{2,3}$ = 5), C_2-H], 7.3-6.68 (5H, m, Ph, C_3-H), 3.45 (3H, s, NMe); mass calculated for $C_{12}H_9DN_2{}^{32}S$, 215.0626; found, 215.0620. Extraction of silica gel fraction (R_f 0.97) gave 2-*n*-butyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXIII, R = Me, R^2 = *n*-Bu) as a yellow oil (0.009 g, 6.7%) identical (nmr) with an authentic sample.

5.12.4.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with *n*-butyllithium and diethyl chlorophosphate

The general procedure outlined in section 5.12.0.0.0 was followed. *n*-Butyllithium (0.32 g, 5 mmol), 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) (1.07 g, 5 mmol) and diethyl chlorophosphate (0.95 g, 5.5 mmol) were stirred at -77° for 1.5 hr and allowed to warm to room temperature over a 2 hr period. The resulting light orange solution was treated with water (50 ml), extracted with dichloromethane (3 x 50 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark reddish-brown oil (1.924 g) of which 0.9 g was subjected to preparative thin-layer chromatography on ten silica gel plates using benzene-ethyl acetate (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.95) gave 2-n-butyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXIIIb) as a light yellow oil (0.019 g, 3%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (R_f 0.41) gave 1-diethylphosphoryl-2-*n*-butyl-10-methyl-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIb) as a bright

yellow oil (0.237 g, 24.8%). ν_{max} (film)(cm^{-1}): 1273 (P=O), 1630 and 1567 (C=C); nmr δ: 7.35-6.68 (4H, m, Ph), 5.91-5.32 (2H, m, C_3-H, C_4-H), 4.52-3.59 [5H, m, C_2-H, $(OC\underline{H_2}CH_3)_2$], 3.36 (3H, s, NMe), 1.92-0.58 [15H, m, *n*-Bu, $(OCH_2C\underline{H_3})_2$]; mass calculated for $C_{20}H_{29}N_2O_3P^{32}S$, 408.1630; found, 408.1635. Extraction of the silica gel fraction (R_f 0.18) gave *4-diethylphosphoryl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine* (CLXXXVIIb) as a bright yellow oil (0.147 g, 17.9%). ν_{max} (film) (cm^{-1}): 1265 (P=O); nmr δ: 8.14 [1H, t($J_{2,3} = J_{2,P^{31}} = 5$), C_2-H], 7.3-6.72 (5H, m, C_3-H, Ph), 4.25 [4H, m, $(OC\underline{H_2}CH_3)_2$], 3.44 (3H, s, NMe), 1.36 [6H, t($J_{CH_2-CH_3}$ = 7), $(OCH_2C\underline{H_3})_2$]; mass calculated for $C_{16}H_{19}N_2O_3P^{32}S$, 350.0850; found, 350.0846. Extraction of the silica gel fraction (R_f 0.86) gave a light yellow oil (0.118 g) which was rechromatographed on one silica gel plate using benzene-ethyl acetate (10:1 v/v) as the development solvent. This gave two fractions (R_f 0.65) and (R_f 0.5). Extraction of the silica gel fraction (R_f 0.65) gave *2-n-butyl-4a-ethyl-10-methyl-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine* (CLXXXVIIIb) as a yellow oil (0.058 g, 8.3%). ν_{max} (film) (cm^{-1}): 1677, 1631 (C=N, C=C); nmr δ: 7.44-6.68 (4H, m, Ph), 6.12 [1H, d($J_{3,4}$ = 10) of d($J_{2,3(4)}$ = 1.75), C_3-H or C_4-H], 5.64 [1H, d($J_{3,4}$ = 10) of d($J_{2,3(4)}$ = 2), C_3-H or C_4-H], 4.18 (1H, m, C_2-H), 3.58 (3H, s, NMe), 2-0.59 (11H, m, *n*-Bu, $C\underline{H_2}CH_3$), 0.7 [3H, t($J_{CH_2-CH_3}$ = 7), $CH_2C\underline{H_3}$]; mass calculated for $C_{18}H_{24}N_2{}^{32}S$, 300.1655; found, 300.1651. Extraction of the silica gel fraction (R_f 0.5) gave 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIb) as a yellow solid (0.033 g, 6.6%) identical (nmr, mp) with an authentic sample.

5.12.5.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-butyllithium and p-fluorobenzoyl chloride

The general procedure outlined in section 5.12.0.0.0 was followed. *n*-Butyllithium (0.32 g, 5 mmol), 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) (1.07 g, 5 mmol) and p-fluorobenzoyl chloride (0.875 g, 5.5 mmol) were stirred at -77° for 1 hr and allowed to warm to room temperature over a 2.5 hr period. The resulting dark red solution was treated with water (60 ml), extracted with dichloromethane (3 x 50 ml), and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark red oil (2.037 g) of which 0.85 g was subjected to preparative thin-layer chromatography on ten silica gel plates using benzene-ethyl acetate (25:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.94) gave 2-*n*-butyl-4-(or 7-)p-fluorobenzoyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLc-2 or 1) a yellow waxy solid (0.02 g, 2.5%), mp 93-96°; ν_{max} (cm^{-1}): 1660 (C=O); nmr δ: 7.8 [2H, d($J_{2',3'}$ = 10) of d($J_{2',F}$ = 6), $C_{2'}$-H], 7.39-6.73 (7H, m, Ph, pyridyl H), 3.5 (3H, s, NMe), 2.72 [2H, t($J_{CH_2-CH_2C_2H_5}$ = 7), $C\underline{H_2}C_3H_7$], 2.01-0.72 [7H, m, $CH_2C_3\underline{H_7}$]; mass calculated for $C_{23}H_{21}N_2O^{32}SF$, 392.1354; found, 392.1359. Extraction of the silica gel fraction (R_f 0.58) gave a red oil (0.302 g) of which 0.2 g was rechromatographed on four silica gel plates using benzene as the development solvent. This gave two fractions (R_f 0.43) and (R_f 0.31). Extraction of the silica gel fraction (R_f 0.43) gave 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) as a yellow solid (0.03 g, 10.2%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction

(R_f 0.31) gave a red solid which was dissolved in chloroform and precipitated from solution by the addition of methanol. This gave 1,4-(or 7-)di-p-fluorobenzoyl-2-n-butyl-10-methyl-1,2-dihydropyridyl-[3,2-b][1,4]benzothiazine (CLXXXIXc-2 or 1) as a red solid (0.137 g, 35%), mp 84-86° (decomp.); ν_{max} (cm^{-1}): 1681 (C=O), 1635 (C=C); nmr δ: 7.82-6.64 (12H, m, Ph and C_4-H or C_7-H), 6.11-5.6 (2H, m, C_2-H, C_3-H), 3.08 (3H, s, NMe), 2.08-0.77 (9H, m, n-Bu); mass calculated for $C_{30}H_{26}N_2O_2{}^{32}SF_2$, 516.1677; found, 516.1680.

5.12.6.0.0 Reaction of 10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine with n-butyllithium and trifluoromethanesulfonyl chloride

The general procedure outlined in section 5.12.0.0.0 was followed. n-Butyllithium (0.16 g, 2.5 mmol), 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) (0.535 g, 2.5 mmol) and trifluoromethanesulfonyl chloride (0.463 g, 2.75 mmol) were stirred at -77° for 1 hr and allowed to warm to room temperature over a 1.5 hr period. The resulting dark yellow solution was treated with water (50 ml), extracted with dichloromethane (3 x 50 ml), and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a brownish-red oil (0.819 g) of which 0.8 g was subjected to preparative thin-layer chromatography on twelve silica gel plates using benzene-ethyl acetate (10:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.97) gave 2-n-butyl-10-methyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXIIId) as a yellow oil (0.293 g, 44.4%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (R_f 0.64) gave a yellow semi-solid (0.143 g) which was rechromatographed

on two silica gel plates using benzene as the development solvent. This gave two fractions (R_f 0.41) and (R_f 0.28). Extraction of the silica gel fraction (R_f 0.28) gave 10-methyl-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIb) as a light yellow solid (0.027 g, 5.2%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (R_f 0.41) gave 4-chloro-10-methyl-10H-pyrido[3,2-b]-[1,4]benzothiazine (CLXXXVIId) as a light yellow solid (0.09 g, 14.5%), mp 74-75°; nmr δ: 7.89 [1H, d($J_{2,3}$ = 5.5), C_2-H], 7.33-6.8 (4H, m, Ph), 6.76 [1H, d($J_{2,3}$ = 5.5), C_3-H], 3.39 (3H, s, NMe); mass calculated for $C_{12}H_9N_2{}^{32}S^{37}Cl$, 250.0144; found, 250.0141; mass calculated for $C_{12}H_9N_2{}^{32}S^{35}Cl$, 248.0174; found, 248.0168. Analytical calculated for $C_{12}H_9N_2SCl$: C, 57.95; H, 3.65; N, 11.26; S, 12.88; found, C, 57.95; H, 3.73; N, 11.24; S, 12.83.

5.13.0.0.0 Reaction of 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with *n*-butyllithium and methyl chloroformate

In a dry nitrogen atmosphere *n*-butyllithium (0.165 g, 2.58 mmol) was added dropwise with stirring to a solution of 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIc) (0.7 g, 2.58 mmol) in anhydrous tetrahydrofuran (30 ml) at 0°. The resulting dark brown solution was stirred at 0° for 40 min, cooled to -77°, and methyl chloroformate (0.488 g, 5.17 mmol) in tetrahydrofuran (2 ml) was added dropwise. The resulting solution was stirred at -77° for 0.5 hr and allowed to warm to room temperature over a 3.5 hr period. The resulting dark brown solution was treated with water

(50 ml), extracted with ether (3 x 100 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark brown oil (0.711 g) of which 0.6 g was subjected to preparative thin-layer chromatography on seven silica gel plates using benzene-ether (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.40) gave 10-(2-N-methoxycarbonyl-2-N-methylaminoethyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine (CLXLIV) as a dark yellow oil (0.167 g, 24.4%). ν_{max} (film) (cm^{-1}): 1710 (C=O); nmr δ: 8 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 1.75), C_2-H], 7.34-6.59 (6H, m, Ph, C_3-H, C_4-H), 4.29 [2H, m, $C\underline{H_2}CH_2NCH_3(CO_2Me)$], 3.95-3.51 [2H, m, $CH_2C\underline{H_2}NCH_3(CO_2Me)$], 3.74 (3H, s, OMe), 3.04 (3H, s, NMe); mass calculated for $C_{16}H_{17}N_3O_2{}^{32}S$, 315.1038; found, 315.1042. Extraction of the silica gel fraction (R_f 0.15) gave 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXIIc) as a light brown oil (0.19 g, 32.1%) identical (nmr) with an authentic sample.

5.14.0.0.0 Reaction of 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with *n*-butyllithium

In a dry nitrogen atmosphere 10-(2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIc) (0.8 g, 2.95 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise with stirring to a solution of *n*-butyllithium (0.567 g, 8.86 mmol) in anhydrous tetrahydrofuran (50 ml) at 0°. This solution was stirred at 0° for 1 hr and allowed to warm to room temperature over a 1 hr period. The resulting dark brown solution was treated with water (50 ml), extracted with ether (2 x 100 ml) and dried (Na_2SO_4). Evaporation

of the solvent *in vacuo* gave a reddish-brown oil (1.084 g) of which 0.33 g was subjected to preparative thin-layer chromatography on seven silica gel plates using benzene-ether (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 1) gave a dark yellow oil which was rechromatographed on one silica gel plate using petroleum ether (bp 35-60°) as the development solvent. This gave a single fraction (R_f 0.05) which was extracted to give 10-*n*-hexyl-10H-pyrido[3,2-b][1,4]benzothiazine (CLXLV) as a yellow oil (0.066 g, 25.9%). nmr δ: 8.01 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 1.75), C_2-H], 7.38-6.59 (6H, m, Ph, C_3-H, C_4-H), 4.1 [2H, t($J_{NCH_2\text{-}CH_2C_4H_9}$ = 7), $NC\underline{H_2}C_5H_{11}$], 2.11-0.65 (11H, m, $NCH_2C_5\underline{H_{11}}$]; mass calculated for $C_{17}H_{20}N_2{}^{32}S$, 284.1343; found, 284.1347.

5.15.0.0.0 The reaction of 10-(3-dimethylaminopropyl)-10H-pyrido-[3,2-b][1,4]benzothiazine with *n*-butyllithium and subsequent reaction with electrophilic reagents

5.15.1.0.0 Reaction of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with *n*-butyllithium and methyl chloroformate

In a dry nitrogen atmosphere *n*-butyllithium (0.18 g, 2.81 mmol) was added dropwise with stirring to a solution of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) (0.8 g, 2.81 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting greenish-brown solution was stirred at 0° for 1 hr, cooled to -77°, and methyl chloroformate (0.318 g, 3.37 mmol) in anhydrous

tetrahydrofuran (2 ml) was added dropwise. The reaction was stirred at -77° for 1 hr and allowed to warm to room temperature over a 2 hr period. The resulting light brown solution was treated with water (75 ml), extracted with dichloromethane (4 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a brown oil (1.067 g) of which 0.65 g was subjected to preparative thin-layer chromatography on twelve silica gel plates using benzene-ethyl acetate (2:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.15) gave a yellow oil which was rechromatographed on four silica gel plates using ether-methanol (3:1 v/v) as the development solvent. This gave a single fraction (R_f 0.87) which was extracted to give *1-methoxycarbonyl-2-n-butyl-10-(3-dimethylaminopropyl)-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine* (CLXXVIIIe) as a yellow oil (0.215 g, 31.4%). Alternatively, chromatography of the reaction product on a 2.5 x 28 cm silica gel column and elution with ether (800 ml) gave 1-methoxycarbonyl-2-*n*-butyl-10-(3-dimethylaminopropyl)-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIe) as a yellow oil (54.5%). ν_{max} (film) (cm^{-1}): 1724 (C=O), 1635 (C=C); nmr δ: 7.34-6.7 (4H, m, Ph), 5.93-5.42 (2H, m, C_3-H, C_4-H), 4.79 (1H, m, C_2-H), 3.88-3.52 [2H, m, $\underline{CH_2}(CH_2)_2N(Me)_2$], 3.69 (3H, s, OMe), 2.45-2.14 [2H, m, $(CH_2)_2\underline{CH_2}N(Me)_2$], 2.14 [6H, s, $N(Me)_2$], 2-0.69 [11H, m, *n*-Bu, $CH_2\underline{CH_2}CH_2N(Me)_2$]; mass calculated for $C_{22}H_{31}N_3O_2{}^{32}S$, 401.2130; found, 401.2135. Extraction of the silica gel fraction (R_f 0.07) gave a yellowish-brown oil (0.293 g) which was rechromatographed on four silica gel plates using chloroform-methanol (5:1 v/v) as the development solvent. This gave two fractions (R_f 0.53) and

(R_f 0.45). Extraction of the silica gel fraction (R_f 0.53) gave 4-methoxycarbonyl-10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]-benzothiazine (CLXXXVIIe) as a bright yellow oil (0.044 g, 7.5%). ν_{max} (film) (cm^{-1}): 1731 (C=O); nmr δ: 7.98 [1H, d($J_{2,3}$ = 5], 7.32-6.64 (5H, m, Ph, C_3-H), 4.01 [2H, m, $\underline{CH_2}(CH_2)_2N(Me)_2$], 3.9 (3H, s, OMe), 2.6-1.7 [4H, m, $CH_2(\underline{CH_2})_2N(Me)_2$], 2.2 [6H, s, $N(Me)_2$]; mass calculated for $C_{18}H_{21}N_3O_2{}^{32}S$, 343.1350; found, 343.1348. Extraction of the silica gel fraction (R_f 0.45) gave 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) as a light yellow oil (0.06 g, 12.3%) identical (nmr) with an authentic sample.

5.15.2.0.0 Reaction of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with n-butyllithium and diethyl chlorophosphate

In a dry nitrogen atmosphere n-butyllithium (0.213 g, 3.33 mmol) was added dropwise with stirring to a solution of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) (0.79 g, 2.77 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting greenish-brown solution was stirred at 0° for 45 min, allowed to warm to room temperature over a 0.5 hr period, cooled to -77°, and diethyl chlorophosphate (0.575 g, 3.33 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise. The reaction was stirred at -77° for 1.5 hr and allowed to warm to room temperature over a 2 hr period. The resulting dark yellow solution was treated with water (100 ml), extracted with chloroform (7 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a light brown oil (1.309 g)

of which 0.72 g was subjected to preparative thin-layer chromatography on ten silica gel plates using chloroform-methanol (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.87) gave *1-diethylphosphoryl-2-n-butyl-10-(3-dimethylaminopropyl)-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine* (CLXXVIIIf) as a dark yellow oil (0.122 g, 16.7%). ν_{max} (film) (cm^{-1}): 1271 (P=O), 1629 and 1568 (C=C); nmr δ: 7.38-6.67 (4H, m, Ph), 5.95-5.4 (2H, m, C_3-H, C_4-H), 4.43 (1H, m, C_2-H), 4.32-3.53 [6H, m, $(OC\underline{H_2}CH_3)_2$, $C\underline{H_2}(CH_2)_2N(Me)_2$], 2.55-2.12 [2H, m, $(CH_2)_2C\underline{H_2}N(Me)_2$], 2.12 [6H, s, $N(Me)_2$], 2.03-0.78 [17H, m, *n*-Bu, $CH_2C\underline{H_2}CH_2N(Me)_2$, $(OCH_2C\underline{H_3})_2$]; mass calculated for $C_{24}H_{38}N_3O_3P^{32}S$, 479.2363; found, 479.2354. Extraction of the silica gel fraction (R_f 0.55) gave *2-n-butyl-4a-ethyl-10-(3-dimethylaminopropyl)-2,4a-dihydropyridyl[3,2-b][1,4]benzothiazine* (CLXXXVIIIf) as a yellow oil (0.014 g, 2.5%). ν_{max} (film) (cm^{-1}): 1629 (C=N, C=C); nmr δ: 7.35-6.9 (4H, m, Ph), 6.1 [1H, d($J_{3,4}$ = 10) of d($J_{2,3(4)}$ = 1.75), C_3-H or C_4-H], 5.55 [1H, d($J_{3,4}$ = 10) of d($J_{2,3(4)}$ = 2), C_3-H or C_4-H], 4.5-3.6 [3H, m, C_2-H, $C\underline{H_2}(CH_2)_2N(Me)_2$], 2.2 [6H, s, $N(Me)_2$], 2.6-0.72 [18H, m, *n*-Bu, Et, $CH_2(C\underline{H_2})_2N(Me)_2$]; mass calculated for $C_{22}H_{33}N_3{}^{32}S$, 371.2388; found, 371.2389. Extraction of the silica gel fraction (R_f 0.5) gave *4-diethylphosphoryl-10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine* (CLXXXVIIf) as a yellow oil (0.06 g, 9.3%). ν_{max} (film) (cm^{-1}): 1266 (P=O); nmr δ: 8.09 [1H, t($J_{2,3} = J_{2,p^{31}}$ = 5), C_2-H], 7.3-6.72 (5H, m, C_3-H, Ph), 4.5-3.74 [6H, m, $(OC\underline{H_2}CH_3)$, $C\underline{H_2}(CH_2)_2$ $N(Me)_2$], 2.65-1.62 [4H, m, $CH_2(C\underline{H_2})_2$ $N(Me)_2$], 2.22 [6H, s, $N(Me)_2$], 1.32 [6H, t($J_{CH_2-CH_3}$ = 7), $(OCH_2C\underline{H_3})_2$]; mass calculated for $C_{20}H_{28}N_3O_3P^{32}S$, 421.1582; found, 421.1595.

Extraction of silica gel fraction (R_f 0.41) gave a brown oil (0.11 g) which was rechromatographed on two silica gel plates using chloroform-methanol (2:1) as the development solvent. This gave a single fraction (R_f 0.64) which was extracted to give 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) as a yellow oil (0.056 g, 12.9%) identical (nmr) with an authentic sample.

5.15.3.0.0 Reaction of 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with *n*-butyllithium and trifluoromethanesulfonyl chloride

In a dry nitrogen atmosphere *n*-butyllithium (0.122 g, 1.91 mmol) was added dropwise with stirring to a solution of 10-(3-dimethylamino-propyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) (0.543 g, 1.91 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting greenish-brown solution was stirred at 0° for 1 hr, cooled to -77°, and trifluoromethanesulfonyl chloride (0.385 g, 2.29 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise. The reaction was stirred at -77° for 0.5 hr and allowed to warm to room temperature over a 2 hr period. The resulting lime green solution was treated with water (75 ml), extracted with dichloromethane (6 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a brown oil (0.683 g) of which 0.6 g was subjected to preparative thin-layer chromatography on nine silica gel plates using chloroform-methanol (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.76) gave *2-n-butyl-10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]-benzothiazine* (CLXXXIIIg) as a yellow oil (0.158 g, 27.7%). nmr δ:

7.4-6.74 (4H, m, Ph), 7.1 [1H, d($J_{3,4}$ = 8), C_4-H], 6.57 [1H, d($J_{3,4}$ = 8), C_3-H], 4.1 [2H, t($J_{CH_2-CH_2}$ = 7), $C\underline{H_2}(CH_2)_2N(Me)_2$], 2.81-0.69 [13H, m, _n_-Bu, $CH_2(C\underline{H_2})_2N(Me)_2$], 2.35 [6H, s, $N(Me)_2$]; mass calculated for $C_{20}H_{27}N_3{}^{32}S$, 341.1920; found, 341.1924. Extraction of the silica gel fraction (R_f 0.46) gave a yellow oil (0.087 g) which was rechromatographed on two silica gel plates using chloroform-methanol (5:1 v/v) as the development solvent. This gave two fractions (R_f 0.58) and (R_f 0.5). Extraction of the silica gel fraction (R_f 0.5) gave 10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIId) as a yellow oil (0.015 g, 3.1%) identical (nmr) with an authentic sample. Extraction of the silica gel fraction (R_f 0.58) gave _4-chloro-10-(3-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine_ (CLXXXVIIg) as a yellow oil (0.051 g, 8.3%). nmr δ: 7.82 [1H, d($J_{2,3}$ = 5.5), C_2-H], 7.29-6.8 (4H, m, Ph), 6.74 [1H, d($J_{2,3}$ = 5.5), C_3-H], 4.02 [2H, t($J_{CH_2-CH_2}$ = 7), $C\underline{H_2}(CH_2)_2N(Me)_2$], 2.57-1.76 [4H, m, $CH_2(C\underline{H_2})_2N(Me)_2$], 2.2 [6H, s, $N(Me)_2$]; mass calculated for $C_{16}H_{18}N_3{}^{32}S^{37}Cl$, 321.0877; found, 321.0867; mass calculated for $C_{16}H_{18}N_3{}^{32}S^{35}Cl$, 319.0907; found, 319.0898.

5.16.0.0 The reaction of 10-(2-dimethylaminopropyl)-10H-pyrido-[3,2-b][1,4]benzothiazine with *n*-butyllithium and subsequent reaction with electrophilic reagents

5.16.1.0.0 Reaction of 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with *n*-butyllithium and diethyl chlorophosphate

In a dry nitrogen atmosphere *n*-butyllithium (0.162 g, 2.53 mmol) was added dropwise with stirring to a solution of 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIe) (0.72 g, 2.53 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting dark brown solution was stirred at 0° for 1 hr, cooled to -77°, and diethyl chlorophosphate (0.524 g, 3.03 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise. The reaction was stirred at -77° for 1 hr and allowed to warm to room temperature over a 2 hr period. The resulting light orange solution was treated with water (100 ml), extracted with chloroform (6 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark reddish-brown (0.984 g) of which 0.9 g was subjected to preparative thin-layer chromatography on ten silica gel plates using chloroform-methanol (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.93) gave a yellow oil (0.256 g) which was rechromatographed on four silica gel plates using chloroform-methanol (5:1 v/v) as the development solvent. This gave two fractions (R_f 0.88) and (R_f 0.72). Extraction of the silica gel fraction (R_f 0.88) gave 1-diethylphosphoryl-2-*n*-butyl-10-(2-dimethylaminopropyl)-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine

(CLXXVIIIh) as a yellow oil (0.156 g, 14.1%). ν_{max} (film) (cm^{-1}): 1270 (P=O), 1630 and 1565 (C=C); nmr δ: 7.23-6.8 (4H, m, Ph), 5.92-5.4 (2H, m, C_3-H, C_4-H), 4.67-3.3 [7H, m, C_2-H, $(OC\underline{H_2}CH_3)_2$, CH_2], 2.7 (1H, m, CH), 2.23 [6H, s, $N(Me)_2$], 1.86-0.71 [15H, m, *n*-Bu, $(OCH_2C\underline{H_3})_2$], 0.98 [3H, d($J_{CH_3CH}$ = 6.5), CH_3]; mass calculated for $C_{24}H_{38}N_3O_3P^{32}S$, 479.2363; found, 479.2369. Extraction of the silica gel fraction (R_f 0.72) gave *2-n-butyl-10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine* (CLXXXIIIh) as a yellow oil (0.019 g, 2.4%). nmr δ: 7.38-6.5 (6H, m, Ph, C_2-H, C_3-H), 4.28 [2H, d(J_{CH_2-CH} = 6.5), CH_2], 3.1 (1H, m, CH), 2.64 [2H, d($J_{CH_2-CH_2C_2H_5}$ = 7), $C\underline{H_2}C_3H_7$], 2.38 [6H, s, $N(Me)_2$], 1.86-0.7 [7H, m, $CH_2C_3\underline{H_7}$], 1.06 [3H, d(J_{CH_3-CH} = 6.5, CH_3]; mass calculated for $C_{20}H_{27}N_3{}^{32}S$, 341.1920; found, 341.1917. Extraction of silica gel fraction (R_f 0.61) gave a yellow oil (0.094 g) which was rechromatographed on one silica gel plate using chloroform-methanol (5:1 v/v) as the development solvent. This gave a single fraction (R_f 0.67) which was extracted to give *4-diethylphosphoryl-10-(2-dimethylaminopropyl)-10H-pyrido-[3,2-b][1,4]benzothiazine* (CLXXXVIIh) as a yellow oil (0.077 g, 7.9%). ν_{max} (film) (cm^{-1}): 1268 (P=O); nmr δ: 8.16 [1H, t($J_{2,3}$ = $J_{2,p^{31}}$ = 5), C_2-H], 7.5-6.89 (5H, m, C_3-H, Ph), 4.51-3.96 [6H, m, CH_2, $(OC\underline{H_2}CH_3)_2$], 3.11 (1H, m, CH), 2.33 [6H, s, $N(Me)_2$], 1.36 [6H, t($J_{CH_2-CH_3}$ = 7), $(OCH_2C\underline{H_3})_2$], 1.07 [3H, d($J_{CH_3-CH}$ = 6.5), CH_3]; mass calculated for $C_{20}H_{28}N_3O_3P^{32}S$, 421.1583; found, 421.1580.

5.16.2.0.0 Reaction of 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b]-[1,4]benzothiazine with n-butyllithium and methyl chloroformate

In a dry nitrogen atmosphere n-butyllithium (0.162 g, 2.53 mmol) was added dropwise with stirring to a solution of 10-(2-dimethylamino-propyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIe) (0.072 g, 2.53 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting dark brown solution was stirred at 0° for 1 hr, cooled to -77°, and methyl chloroformate (0.286 g, 3.03 mmol) in anhydrous tetrahydro-furan (2 ml) was added dropwise. The reaction was stirred at -77° for 1 hr and allowed to warm to room temperature over a 2 hr period. The resulting light brown solution was treated with water (100 ml), extracted with chloroform (5 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a dark reddish-brown oil (1.038 g) of which 0.9 g was subjected to preparative thin-layer chromatography on twelve silica gel plates using ethyl acetate-ether (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.34) gave 1-methoxycarbonyl-2-n-butyl-10-(dimethylaminopropyl)-1,2-dihydropyridyl[3,2-b][1,4]benzothiazine (CLXXVIIIi) as a yellow oil (0.338 g, 38.5%). ν_{max} (film) (cm^{-1}): 1726 (C=O), 1630 (C=C); nmr δ: 7.32-6.74 (4H, m, Ph), 5.96-5.49 (2H, m, C_3-H, C_4-H), 4.9 (1H, m, C_2-H), 3.8-3.4 (2H, m, CH_2), 3.72 (3H, s OMe), 3 (1H, m, CH), 2.3 [6H, s, $N(Me)_2$], 1.88-0.69 (9H, m, n-Bu), 1.07 [3H, d(J_{CH_3-CH} = 6.5), CH_3]; mass calculated for $C_{22}H_{31}N_3O_2{}^{32}S$, 401.2130; found, 401.2146. Extraction of the silica gel fraction (R_f 0.14) gave a dark yellow oil (0.25 g) which was rechromatographed on six silica

gel plates using chloroform-methanol (5:1 v/v) as the development solvent. This gave two fractions (R_f 0.8) and (R_f 0.73). Extraction of silica gel fraction (R_f 0.8) gave 4-methoxycarbonyl-10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXXVIIi) as a yellow oil (0.064 g, 8.5%). ν_{max} (film) (cm^{-1}): 1729 (C=O); nmr δ: 8 [1H, d($J_{2,3}$ = 5), C_2-H], 7.32-6.7 (4H, m, Ph), 7.16 [1H, d($J_{2,3}$ = 5), C_3-H], 4.3-4.08 (2H, m, CH_2), 3.9 (3H, s, OMe), 3.08 (1H, m, CH), 2.29 [6H, s, $N(Me)_2$], 1 [3H, d($J_{CH_3\text{-}CH}$ = 6.5), CH_3]; mass calculated for $C_{18}H_{21}N_3O_2{}^{32}S$, 343.1350; found, 343.1347. Extraction of the silica gel fraction (R_f 0.73) gave 10-(2-dimethylaminopropyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIe) as a yellow oil (0.075 g, 12%) identical (nmr) with an authentic sample.

5.17.0.0.0 Reaction of 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine with n-butyllithium and methyl chloroformate

In a dry nitrogen atmosphere n-butyllithium (0.202 g, 3.16 mmol) was added dropwise with stirring to a solution of 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIf) (0.9 g, 3.16 mmol) in anhydrous tetrahydrofuran (125 ml) at 0°. The resulting dark brown solution was stirred at 0° for 1.5 hr, cooled to -77°, and methyl chloroformate (0.358 g, 3.79 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise. The reaction was stirred at -77° for 1 hr and allowed to warm to room temperature over a 2 hr period. The resulting orange-red suspension was treated with water (100 ml), extracted with chloroform (8 x 50 ml) and dried (Na_2SO_4).

Evaporation of the solvent in vacuo gave a brown oil (0.856 g) of which 0.8 g was subjected to preparative thin-layer chromatography on twelve silica gel plates using benzene-ether (1:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.54) gave 10H-pyrido[3,2-b][1,4]benzothiazine (CLXXIIa) as a yellow solid (0.09 g, 15.2%) identical (nmr, mp) with an authentic sample.

5.18.0.0.0 The reaction of aromatic amines with 2-bromopyridine

5.18.1.0.0 Reaction of aniline with 2-bromopyridine

Aniline (5.86 g, 63 mmol) and 2-bromopyridine (4.97 g, 31.5 mmol) were boiled under reflux for 1.5 hr. The resulting black tar was treated with water (100 ml) and basified to pH 8.5 using potassium carbonate. The precipitate which formed was filtered and a methanolic (100 ml) solution of the precipitate was decolorized using activated charcoal. This was filtered and the solvent evaporated in vacuo to give a yellow solid which was recrystallized from absolute ethanol to give 2-anilinopyridine (CCXIIIa) as an off-white solid (4.522 g, 84.4%), mp 105-106° (reported[245], mp 105-108°). ν_{max} (cm^{-1}): 3250 (NH); nmr δ: 8.2 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 2) of d($J_{2,5}$ = 1), C_2-H], 7.81-6.5 (9H, m, Ph, pyridyl H, NH, exchanges with deuterium oxide); mass calculated for $C_{11}H_{10}N_2$, 170.0842; found, 170.0832.

5.18.2.0.0 Reaction of N-methylaniline with 2-bromopyridine

In a dry nitrogen atmosphere N-methylaniline (1.079, 10 mmol) was added to lithium amide (0.23 g, 10 mmol) at room temperature.

This was stirred at room temperature for 0.5 hr, cooled to 0°, and 2-bromopyridine (1.58 g, 10 mmol) was added dropwise. The resulting dark brown solution was stirred at 0° for 1 hr, allowed to warm to room temperature over a 1 hr period, and boiled under reflux for 4 hr. The reaction was stirred overnight at room temperature for 16 hr, treated with water (15 ml), extracted with dichloromethane (3 x 20 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark brown oil which was subjected to vacuum distillation. The first fraction (0.201 g) (29°/0.13 mm) gave a mixture of N-methylaniline (9.4%) and 2-bromopyridine (6.3%) while the second fraction (86-88°/ 0.13 mm) gave 2-(N-methylanilino)-pyridine (CCXIIIb) as a light yellow oil (1.362 g, 74%), (reported[246], bp 147-8°/10 mm). nmr δ: 8.28 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 2) of d($J_{2,5}$ = 1), C_2-H], 7.6-6.99 (6H, m, Ph, pyridyl H), 6.73-6.40 (2H, m, Ph, pyridyl H), 3.42 (3H, s, CH_3); mass calculated for $C_{12}H_{12}N_2$, 184.0998; found, 184.0983.

5.19.0.0.0 The reaction of 2-anilinopyridine with *n*-butyllithium and electrophilic reagents

5.19.1.0.0 Reaction of 2-anilinopyridine with *n*-butyllithium and methyl chloroformate

In a dry nitrogen atmosphere *n*-butyllithium (0.512 g, 8 mmol) was added dropwise with stirring to a solution of 2-anilinopyridine (CCXIIIa) (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (100 ml) at -77°. The resulting dark yellow solution was stirred at -77° for 0.5 hr and methyl chloroformate (1.134 g, 12 mmol) was added dropwise.

This was stirred at -77° for 0.5 hr and allowed to warm to room temperature over a 1 hr period. The resulting light yellow solution was treated with water (50 ml), extracted with dichloromethane (3 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a yellow solid (1.355 g) of which 0.22 g was subjected to preparative thin-layer chromatography on three silica gel plates using benzene-ether (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.38) gave 2-(N-methoxycarbonylanilino)-pyridine (CCXVI) as an off-white solid (0.138 g, 93.2%), mp 93-4°; ν_{max} (cm^{-1}): 1732 (C=O); nmr δ: 8.42 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 2) of d($J_{2,5}$ = 1), C_2-H], 8.0-6.88 (8H, m, Ph, pyridyl H), 3.73 (3H, s, OMe); mass calculated for $C_{13}H_{12}N_2O_2$, 228.0896; found, 228.0884.

5.19.2.0.0 Reaction of 2-anilinopyridine with n-butyllithium and acetyl chloride

In a dry nitrogen atmosphere n-butyllithium (0.512 g, 8 mmol) was added dropwise with stirring to a solution of 2-anilinopyridine (CCXIIIa) (0.68 g, 4 mmol) in anhydrous tetrahydrofuran (100 ml) at -77°. The resulting dark yellow solution was stirred at -77° for 0.5 hr and acetyl chloride (0.942 g, 12 mmol) was added dropwise. This was stirred at -77° for 1 hr and allowed to warm to room temperature over a 1 hr period. The resulting medium brown solution was treated with water (50 ml), extracted with dichloromethane (3 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a brown

oil (1.042 g) of which 0.2 g was subjected to preparative thin-layer chromatography on three silica gel plates using ether-benzene (5:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.44) gave 2-(N-acetylanilino)-pyridine (CCXV) as a yellow oil[308] (0.149 g, 91.5%). ν_{max} (film) (cm^{-1}): 1685 (C=O); nmr δ: 8.45 [1H, d($J_{2,3}$ = 5) of d($J_{2,4}$ = 2) of d($J_{2,5}$ = 1), C_2-H], 7.91-6.92 (8H, m, Ph, pyridyl H), 2.1 (3H, s, CH_3); mass calculated for $C_{13}H_{12}N_2O$, 212.0947; found, 212.0947.

5.20.0.0.0 Reaction of 2-(N-acetylanilino)-pyridine with n-butyllithium and methyl chloroformate

In a dry nitrogen atmosphere n-butyllithium (0.384 g, 6 mmol) was added dropwise with stirring to a solution of 2-(N-acetylanilino)-pyridine (CCXV) (0.636 g, 3 mmol) in anhydrous tetrahydrofuran (100 ml) at 0°. The resulting light brown solution was stirred at 0° for 1.25 hr and methyl chloroformate (0.851 g, 9 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise. This solution was stirred at 0° for 0.5 hr and allowed to warm to room temperature over a 1 hr period. The resulting brown solution was treated with water (50 ml), extracted with dichloromethane (3 x 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a dark brown oil (1.334 g) of which 0.15 g was subjected to preparative thin-layer chromatography on two silica gel plates using ether-methanol (25:1 v/v) as the development solvent. Extraction of the silica gel fraction (R_f 0.82) gave 2-(N-methoxycarbonylanilino)-pyridine (CCXVI) as a light yellow solid (0.061 g, 79.2%) identical (nmr) with an authentic sample.

6.0.0.0.0 Bibliography

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